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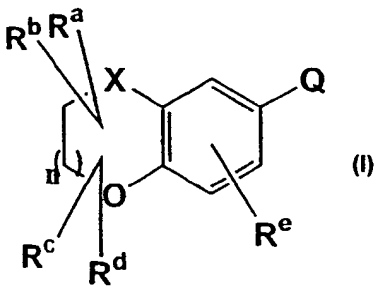


(I)

(57) Abstract: A compound of the general formula (I) and method for preparing and using the compound of formula (I).

NOVEL HETEROCYCLIC COMPOUNDS USEFUL FOR INFLAMMATORY ALLERGIC DISORDERS; PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Field Of The Invention

The present invention relates to novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them. The present invention more particularly relates to novel PDE4 inhibitors of the formula 1, their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and the pharmaceutical compositions containing them.

The present invention also relates to a process for the preparation of the above said novel compounds of the formula 1 as defined below. The compounds of general formula 1, more particularly, down regulate or inhibit the production of TNF-α as they are PDE4 inhibitors and therefore are useful in the treatment of variety of allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjuctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. The compounds of the present invention are particularly useful for the treatment of asthma.

Background Of The Invention

Airway inflammation characterizes a number of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include edema of airway walls, infiltration of inflammatory cells into the lung, production of various inflammatory mediators and increased mucous production. The airways of asthmatic patients are infiltrated by inflammatory leukocytes, of which the eosinophil is the most prominent component. The magnitude of asthmatic reactions are correlated with the number of eosinophils present in lungs. The accumulation of eosinophils are found dramatically in the lungs of asthmatic patients although they are very few in the lungs of a normal individual. They are capable of lysing and activating cells and destroying tissues. When activated, they synthesize and release inflammatory cytokines such as IL-1, IL-3, TNF-α and inflammatory mediators such as PAF, LTD4 and relative oxygen species that can produce edema, bronchoconstriction. Tumor necrosis factor (TNF-α) was also known to be involved in the pathogenesis of a number of autoimmune and inflammatory diseases. Consequently, manipulation of the cytokine signaling or biosynthetic pathways associated with these proteins may provide therapeutic benefit in those disease states. It has been well demonstrated that TNF-α production in pro-inflammatory cells becomes attenuated by an elevation of intracellular cyclic adenosine 3',5'-monophosphate(cAMP). This second messenger is regulated by the phosphodiesterase(PDE) family of enzymes. The phosphodiesterase enzymes play an integral role in cell signaling mechanisms by hydrolyzing cAMP and cGMP to their inactive 5' forms. Inhibition of PDE enzymes thus results in an elevation of cAMP and /or cGMP levels and alters intracellular responses to extra cellular signals by affecting the processes mediated by cyclic nucleotides. Since eosinophils

are believed to be a critical proinflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma [Rogers.D.F., Giembycz.M.A., *Trends Pharmacol. Sci.*, 19, 160-164(1998); Barnes,P.J., *Trends Pharmacol.Sci.*, 19,415-423(1998)].

The mammalian cyclic nucleotide phosphodiesterases(PDEs) are classified into ten families on the basis of their amino acid sequences and/or DNA sequence, substrate specificity and sensitivity to pharmacological agents [Soderling,S.H., Bayuga,S.J., and Beavo,J.A., *Proc. Natl. Acad. Sci., USA*,96,7071-7076(1999); Fujishige, K, Kotera, J., Michibata, H., Yuasa, K., Takebayashi,Si, Okamura,K. and Omori,K., *J.Biol.Chem.*,.,274, 18438-18445(1999)]. Many cell types express more than one PDE and distribution of isoenzymes between the cells varies markedly. Therefore development of highly isoenzyme selective PDE inhibitors provide a unique opportunity for selective manipulation of various pathophysiological processes.

Phosphodiesterase type 4 (PDE4) is an enzyme which regulates activities in cells which lead to inflammation in the lungs. PDE4, a cAMP-specific and Ca^{+2}-independent enzyme, is a key isozyme in the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes and lymphocytes. The association between cAMP elevation in inflammatory cells with airway smooth muscle relaxation and inhibition of mediator release has led to widespread interest in the design of PDE4 inhibitors[Trophy,T.J., *Am.J.Respir.Crit.Care Med.*, 157, 351-370(1998)]. Excessive or unregulated TNF-a production has been implicated in mediating or exacerbating a number of undesirable physiological conditions such as diseases including osteoarthritis, and other arthritic conditions; septic shock, ecdotoxic shock, respiratory distress syndrome, bone resorption diseases. Since TNF-α also participates in the onset and progress of autoimmune diseases, PDE4

inhibitors may find tremendous utility as therapeutic agents for rheumatoid arthritis, multiple sclerosis and Crohn's disease. [*Nature Medicine*, 1, 211-214(19195) and *ibid.*, 244-248]. TNF-α is also reported to be a factor of insulin-resistant diabetes because it declines the phosphorylating mechanism of insulin receptors of muscle and fat cells [*J.clin.Invest.*, 94, 1543-1549(1994)].

Interest in the drugs capable of selective inhibition of PDE 4 has taken much attention due to several factors such as (a) the tissue distribution of PDE-4 strongly suggested that the pathologies related to the central nervous and immune systems could be treated through the selective PDE 4 inhibitors (b) the increase in intracellular cAMP concentration, the obvious biochemical consequence of PDE-4 inhibition, has been well characterized in immuno-competent cells where it acts as a deactivating signal.

Recently four human cDNA isoforms of PDE-4 (PDE4-A,B,C,D) were identified. mRNA for all these four isoforms was expressed in human lungs. PDE 4-A, B and D were expressed in eosinophils. Of these gene families, PDE-4 characterized as the cAMP-specific gene family has been shown to predominate in pro-inflammatory human lymphoid and myeloid lineage cells.

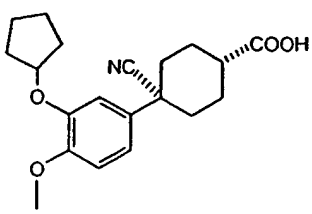
It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation which in turn inhibits the production and release of pro-inflammatory cytokines such as TNF-. Since eosinophils are believed to be a critical pro-inflammatory target for asthma, identification of the expression of PDE 4 gene family in eosinophils led to the PDE 4 as potential therapeutic target for asthma.

Objective Of The Invention

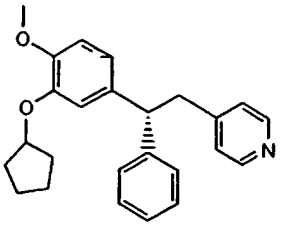
The usefulness of several PDE 4 inhibitors, unfortunately, is limited due to their undesirable side effect profile which include nausea and emesis

(due to action on PDE4 in CNS) and gastric acid secretion due to action on PDE4 in parietal cells in the gut.[Barnette, M.S., Grous, M., Cieslinsky, L.B.,Burman,M., Christensen,S.B., Trophy,T.J.,*J. Pharmacol. Exp. Ther.*, 273,1396-1402(1995)]. One of the earliest PDE4 inhibitors, Rolipram, was withdrawn from the clinical development because of its severe unacceptable side effect profile.[Zeller E.et.al.,*Pharmacopsychiatr.*, 17, 188-190(1984)]. It has recently become apparent, to some extent, the cause of severe side effects of several PDE4 inhibitor molecules in human clinical trials. There exist two binding sites on mammalian PDE4 at which inhibitor molecules bind. Also PDE4 exists in two distinct forms which represent different conformations. They are designated as High affinity Rolipram binding site PDE4H and Low affinity Rolipram binding site PDE4L[Jacobitz,S., McLaughlin,M.M., Livi,G.P., Burman,M., Trophy,T.J., *Mol.Pharmacol* .,50, 891-899(1996)]. It was proved that certain side effects (vomiting and gastric acid secretion) are associated with inhibition of PDE4H whereas some beneficial actions are associated with PDE4L inhibition. It was also found that human recombinant PDE4 exists in 4 isoforms A, B, C and D[Muller,T., Engels,P., Fozard,J.R., *Trends Pharmacol. Sci.*, 17, 294-298(1996)]. Accordingly compounds displaying more PDE4D isoenzyme selectivity over the A, B or C are found to have less amount of side effects than Rolipram [Hughes. B et.al.,, *Br. J. Pharmacol.* **1996**, 118, 1183-1191]. Therefore selective inhibitors of PDE4 isozymes would have therapeutic effects in inflammatory diseases such as asthma and other respiratory diseases.

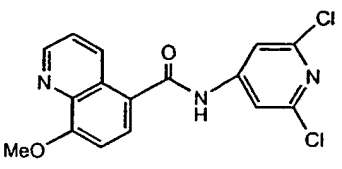
Although several research groups all over the world are working in this direction for achieving the desired highly selective PDE4 isozyme inhibitors, so far the success is limited. Among the various compounds which showed clinically proven PDE 4 inhibition,



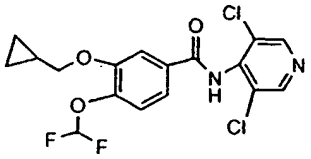
ARIFLO 2



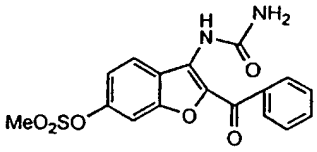
CDP-840 3



D-4418 4

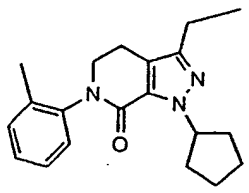


Roflumilast



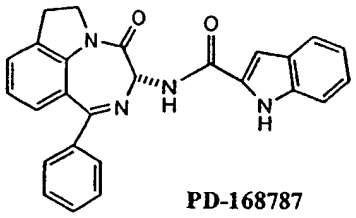
Bay-19-8004

"Ariflo" of the formula 2 (Smith Kline Beecham's compound), Byk gulden's Roflumilast and Bayer's Bay-19-8004 has reached advanced stage of human clinical trials. Some of the other compounds which have shown potent PDE4 inhibitory activity are CDP-840 of the formula 3 (Cellthech's compond), D-4418 of the formula 4 (Schering-Plough's compound) , CP-220,629 of the formula 5 (Pfizer's) , PD- 168787 of the formula 6 (Parke-Davis's compound) and Filaminast of the formula 7(American Home products' compound). However, recently due to various reasons such as efficacy & side effects problems, compounds such as Ariflo, CDP-840, Bay-19-8004 were discontinued from clinical trials for asthma treatment. Other compounds of the formulae 4 & 5 are presently undergoing phase-1 clinical trials.



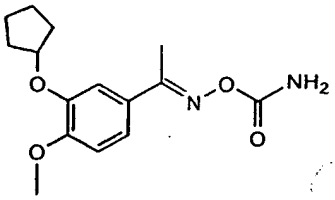
CP - 220,629

5



PD-168787

6



Filaminast

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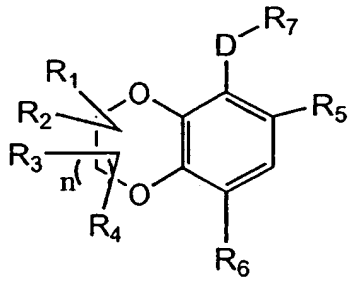
During the course of research aimed at the development of novel anti-asthmatic compounds having potential PDE4 inhibitory activity, we have found in the literature a PCT patent application WO 9822455 and its equivalent version EP 0943613 (published in Sep'1999 by Kyowa Hakko Kogyo Kabushiki Kaishi of Japan), the compounds represented by the general formula **8A** which have potent PDE4 inhibition activity.



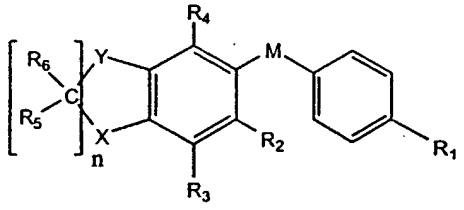
8A

In the componds of the formula **8A**, n represents an integer of 1 to 4; R^1, R^2, R^3 and R^4 are the same or different and represent hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstituted aralkyl, or two groups present on the same carbon atom among R^1, R^2, R^3 and R^4 are combined to represent a saturated carbon ring, two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a saturated carbon ring, together with the two carbon atoms adjacent thereto, or two groups present on the adjacent carbon atoms among R^1, R^2, R^3 and R^4 are combined to represent a single bond; R^5 represents hydrogen or halogen; R^6 represents hydroxy or substituted or unsubstituted lower alkoxy; D represents a group (1) a bond or (2) – $C(R^8)(R^9)$-X-[wherein R^8 and R^9 are the same or different and represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl,

polycycloalkyl, substituted or unsubstituted lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, lower alkanoyloxy ,substituted or unsubstituted lower alkanoyl, cycloalkylcarbonyl, lower alkoxycarbonyl, cyano or halogen, or R^8 and R^9 are combined to represent O, S or NR^{10} (wherein R^{10} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl a substituted or unsubstituted aromatic heterocylcic group, hydroxy, substituted or unsubstituted lower alkoxy, or lower alkanoyloxy); X represents $-CR^{11}R^{12}$ (wherein R^{11} and R^{12} are the same or different and represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted heterocyclic group, substituted or unsubstituted lower alkanoyl, cycloalkylcarbonyl, lower alkoxycarbonyl, or cyano, or represent a single bond together with R^8), S, NR^{13} (wherein R^{13} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or substituted or unsubstitued aralkyl, or represents a single bond together with R^8), or a bond] ; R^7 represents (**a**) substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, a substituted or unsubstituted aromatic heterocyclic group, a substituted or unsubstituted heterocyclic group, or pyridine-N-oxide, (**b**) $-Y-ZR^{14}$ [wherein Y represents substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group; Z represents O,S or NR^{15} (wherein R^{15} represents hydrogen, a substituted or unsubstituted lower alkyl, or represents a substituted or unsubstituted heterocyclic group together with

R^{14}); and R^{14} represents substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group, or represents a substituted or unsubstituted heterocyclic group together with R^{15})], (c) –Y-Z-(CH_2)m-N(R^{16a})R^{16b} (wherein Y and Z have the same meanings as defined above; R^{16a} and R^{16b} are the same or different and represent hydrogen, or substituted or unsubstituted lower alkyl, or R^{16a} and R^{16b} are combined to represent a substituted or unsubstituted heterocylic group; and m represents an integer of 1 to 4); or (**d**) –Y-CON(R^{17a})R^{17b}(wherein Y has the same meaning as defined above; and R^{17a} and R^{17b} are the same or different and represent hydrogen, or substituted or unsubstituted lower alkyl, or R^{17a} and R^{17b} are combined to represent a substituted or unsubstituted heterocyclic group), or a pharmaceutically acceptable salt thereof.

In another US patent application bearing the no. 5,037,825 published in 1991 by Hoffmann-La-Roche , the compounds of the formula **8B** ,



8B

were reported to be useful for the treatment of inflammatory, allergic, rheumatic, and immunological disorders. In the compounds of the formula **8B**, R_1 is hydrogen, acyl, lower alkyl, or -CHO, -CH_2OR_{10}, -CO-R_7,or OR_{13}; R_2, R_3, R_4 are independently hydrogen, lower alkyl, lower alkoxy, or halogen, ; R_5 and R_6 are independently hydrogen or lower alkyl; R_7 is hydroxy, lower alkoxy, or NR_8R_9; R_8 and R_9 are independently hydrogen, or lower alkyl; X and Y are independently >CR_{14},R_{15}, -O-, -S-, >SO, >SO_2 or

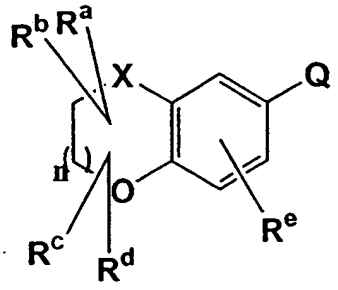
$>NR_{18}$; R_{10} and R_{18} are independently hydrogen, lower alkyl or acyl ; M is -$CR_{11}=CR_{12}$-, -CONH-, or -NH-CO- ; R_{11}, R_{12}, R_{14} and R_{15} are independently hydrogen or lower alkyl, R_{13} is hydrogen, lower alkoxycarbonyl or lower alkyl which can be substituted by amino, mono-alkylamino, di-alkylamino, morphilino, thiomorphilino, or piperazino; and n is 1,2,3 or 4; with the proviso that atleast one of X and Y comprises a hetero atom and n is 1,3 or 4 when X contains a hetero atom, Y is $>C(CH_3)_2$, and R_1 is lower alkyl or CH_2OR_{10} or $-COR_7$; or a salt of a compound of the formula **8B** when R_1 is carboxy.

By a thorough and careful study of the available literature on the PDE4 inhibitory molecules and its structure activity relationship(SAR), we envisaged that the compounds having a combination of structural features of compounds of the formulae **3, 7** and **8** will provide a novel series of heterocyclic compounds which may possess potent PDE4 inhibitory activity with limited side effects.

Accordingly we have prepared a novel series of compounds having the general formula **1** as defined below. We have examined the *in vitro* efficacy of these novel compounds against human PDE4 enzyme and found to show excellent PDE4 enzyme inhibition activity at nanomolar concentrations. The compounds of the present invention are useful as therapeutic agents for inflammatory allergic diseases particularly bronchial asthma, allergic rhinitis and nephritis. Since these compounds also inhibit the production of Tumor Necrosis factor(TNF), they may also find use in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, psoriasis ; diseases of the central nervous system such as depression amnesia, and dermentia cardiac failure, shock, and cerebrovascular disease and the like ; insulin-resistant diabetes and the like.

Summary Of The Invention

Accordingly, the present invention provides novel heterocyclic compounds of the general formula 1,



1

their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of,

wherein n represents an integer of 1 to 3; R^a, R^b, R^c or R^d may be the same or different and represent hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aromatic heterocyclic group, substituted or unsubstituted aralkyl group or two groups present on the same carbon atom among R^a, R^b, R^c, R^d may be combined to represent a optionally substituted 5-8 membered cyclic ring ; or two groups present on the adjacent carbon atoms among R^a,R^b,R^c,R^d may be combined to represent a cyclic ring of 4-8 membered ; or two groups present on the adjacent carbon atoms among R^a,R^b,R^c,R^d may be combined to represent a single bond;

R^e represents hydrogen, halogen, nitro, alkylamino, hydroxyl, substituted or un substituted lower alkyl, substituted or unsubstituted lower alkoxy or two moieties of R^e adjacent to each other are combined together to

form a 5-6 membered cyclic ring optionally containing one hetero atom such as oxygen or nitrogen; X represents $-N(R^f)-$, $-S(O)_m-$, -O- or $-C(R^{g1})(R^{g2})$ wherein R^f is hydrogen, substituted or unsubstituted lower alkyl, $-C(=O)-R^h$ or $C(=O)-O-R^h$ in which R^h is substituted or unsubstituted lower alkyl, substituted or unsub-stituted aryl, substituted or unsubstituted heteroaryl; R^{g1} and R^{g2} are independently hydrogen, hydroxyl, substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy groups; m is an integer of 0, 1 or 2; and

Q represents

(1) a group which represents $-C(R^1)=N-O-(Y)_p-W$ (wherein Y is substituted or optionally substituted lower alkyl, -C(=O), -C(=S), -C(=O)-O, or C(=O)-NH group); p is an integer of 0 or 1;W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups; R^1 is a $-(CH_2)s-Z-Ar^1$ (wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl); and s is zero or the integer 1,2,3,or 4; Z is a bond, -O-, -S, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups;

(2) a group which represents $-CR^1=CR^j-W$ wherein R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted

aryl; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups; and s represents an integer of 0 to 4;

(3) a group which represents $-C(R^1)(R^2)-(CHR^j)-W$ wherein R^j represents hydrogen, substituted or unsubstituted lower alkyl, , substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups ; R^2 represents hydroxyl, substituted or unsubstituted lower alkoxy, $-OC(=O)-R^k$, $-OC(=O)NHR^k$, in which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted mono-cyclic or bicyclic heteroaryl , substituted or unsubstituted aryl); Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. groups; s is an integer of 0 to 4 ; and W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups;

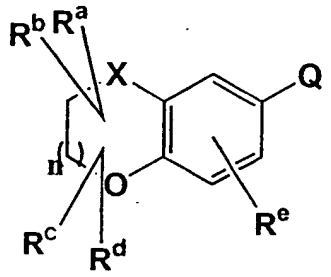
(4) a group represents $-CH(R^1)-L-W$ wherein L represents $-N(R^i)-$, S(O)r-,-O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups and r is an integer of 0,1 or 2 ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -

S-, or N(R^i) (wherein R^i represents hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. groups) and s is an integer of 0 to 4;

(5) a group represents -CONH-$(CH_2)_t$-Ar^2 where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups;

Detailed Description Of The Invention

The present invention particularly provides novel heterocyclic compounds of the formula 1



1

wherein R^a, R^b, R^c, R^d , R^e, R^1, R^2 and W have the meanings described above. The definition of the groups in the formula 1, their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them have the following meanings throughout the present invention.

The term 'lower alkyl' denotes a univalent, branched or straight hydrocarbon chain containing 1 to 8 carbon atoms. Representative of the alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec.butyl, tert.butyl, pentyl, iso pentyl, tert.pentyl, hexyl, isohexyl, octyl and the like.
The term 'lower alkoxy' denotes lower alkyl groups as defined above attached via oxygen linkage to the rest of the molecule. Representative of

those groups are methoxy, ethoxy, isopropoxy, tert.butoxy, hexoxy, heptoxy, octoxy and the like.

The term 'cycloalkyl' denotes having 3 to 10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

The term 'polycycloalkyl' denotes having 4 to 12 carbon atoms, such as bicyclo[3.2.1]octyl, bicyclo[4.3.2]undecyl, adamantyl and noradamantyl and the like.

The term 'lower alkenyl' includes straight-chain or branched alkenyl groups having 2 to 8 carbon atoms, such as vinyl, 1-propenyl, allyl, methacryl, 1-butenyl, crotyl, pentyl, isoprenyl, hexenyl, heptenyl, and octenyl.

The term 'cyclo alkenyl' includes cycloalkenyl groups having 4 to 10 carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl and cyclodecenyl. The term 'aryl' includes phenyl and naphthyl and the like.

The term 'aralkyl' includes aralkyl groups having 7 to 15 carbon atoms, such as benzyl, phenethyl, and naphthylmethyl and the like.

The term 'heteroaryl' group represented in compounds of formula 1 may preferably be selected from pyridyl, quinoline, isoquinoline, indanyl, pyrrole, furan, thiophene, pyrimidine, pyridazinyl, benzofuryl, isobenzofuryl, benzothienyl, indolyl, isoindolyl, benzimidazolyl, benzothiazolyl, quinazolinyl, naphthyridinyl, pyrrolyl, imidazole, benzimidazole, triazine, oxazole, benzoxazole, isoxazole, thiazole, benzathiazole, thiazolidine, and the like.

The term 'heterocyclic' group includes 5-,6- or 7-membered monocyclic heterocyclic groups and condensed heterocyclic groups comprising a 6-membered ring and another 6-memered ring, such as

pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, homopiperidino, homopiperazinyl, tetrahydropyridinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl and the like.

The term 'halogen' or 'halo' represents fluorine, chlorine or bromine and the like.

The substituents in the term 'substituted lower alkyl' group may be the same or different which are selected from lower alkenyl; substituted or unsubstituted cycloalkyl or heterocycloalkyl; substituted or unsubstituted aryl or heteroaryl groups; substituted or unsubstituted cycloalkoxy or heterocycloalkoxy; substituted or unsubstituted phenoxy or aryloxy; substituted or unsubstituted benzyloxy; substituted or unsubstituted lower alkoxy; hydroxyl, formyl, aldoxime, carboxyl, alkoxycarbonyl, lower alkanoyl, substituted or unsubstituted benzoyl; OSO_2R' where R' denotes lower alkyl or aryl groups; halogen, haloalkoxy, cyano, nitro, amino or amido in which the amino group may be mono or di substituted where both the substitutents may be independent or combined together to form a cyclic ring system of a total of 5-6 atoms containing carbon and optionally one or two hetero atoms selected from oxygen, nitrogen or sulfur. The terms lower alkyl, lower alkenyl, lower alkoxy and halogen each have the same meanings as defined above.

The substituents in the term 'substituted lower alkenyl' group may be the same or different which are selected from substituted or unsubstituted cycloalkyl or heterocycloalkyl; substituted or unsubstituted aryl or heteroaryl groups; substituted or unsubstituted cycloalkoxy or heterocycloalkoxy; substituted or unsubstituted phenoxy or aryloxy; substituted or unsubstituted benzyloxy; substituted or unsubstituted lower alkoxy; hydroxyl, carboxyl, alkoxycarbonyl, lower alkanoyl, substituted or unsubstituted benzoyl; OSO_2R' where R' denotes lower alkyl or aryl groups; halogen, haloalkoxy,

cyano, nitro, amino or amido where the amino group may be mono or di substituted in which both the substitutents may be independent or combined together to form a cyclic ring system of a total of 5-6 atoms containing carbon and optionally one or two hetero atoms selected from oxygen, nitrogen or sulfur. The terms lower alkyl, lower alkenyl, lower alkoxy and halogen each have the same meanings as defined above.

The term 'substituted lower alkoxy' denotes 'substituted lower alkyl groups' as defined above attached via oxygen linkage to the rest of the molecule. Representative examples of those groups are 2-hydroxyethoxy, 2-methoxyethoxy, 3-cyanopropoxy, 2-N,N-dimethylaminoethoxy, 3-N,N-diethylaminopropoxy, 4-nitrobutoxy, 2-pyrrolidino-ethoxy, 3-piperidinopropoxy, 2-cyclopropylethoxy, 3-fluoropropoxy, 2-[3'-nitrophenyl] ethoxy, 2-[3-N-methylaminophenyl]ethoxy and the like.

The term 'substituted amino' group used in the present invention refers to amino groups substituted with substituents which can be selected from the groups such as hydroxyl, substituted or unsubstituted lower alkyl, SO_2R" where R" denotes lower alkyl or aryl group; substituted or unsubstituted benzyl or benzoyl; alkoxy, alkoxycarbonyl, amido, amino, alkylamino. Representative examples of such groups are N,N-diethylamino, N-benzylamino, N-benzoylamino, N-carboethoxyamnio, N-chloroethylamino groups. Also both the substituents on the amino group can be combined together to form 5 or 6 membered cyclic ring system represented by pyrrolidino, piperdino, morphilino,piperazino, imidazolino and thiazolidino.

The substituents in the 'substituted cycloalkyl', and 'substituted cycloalkenyl' may be the same or different which are selected from groups such as lower alkyl, lower alkenyl, lower alkoxy, hydroxyl, alkoxycarbonyl, carboxyl, -CONHOH group, 5-membered heterocycles optionally containing hetero atoms such as oxygen, nitrogen, sulfur; phenyl, cyano, nitro, and

halogen in which the lower alkyl, lower alkenyl, lower alkoxy and halogen each have the same meanings as defined above.

The substituents in the 'substituted aryl', 'substituted aromatic heterocyclic' group, 'substituted heterocyclic' group and 'substituted aralkyl' group may be the same or different which are selected from groups such as lower alkyl, hydroxy, lower alkoxy, lower alkoxycarbonyl, SO_2R" where R" denotes lower alkyl or aryl group; haloalkyl, carboxyl, -CONHOH; 5-membered heterocycles optionally containing hetero atoms such as oxygen, nitrogen, sulfur; carbamoyl, trifluoromethyl, amido, cyano, nitro, halogen, amino where the amino group may be mono or di substituted in which both the substitutents are independent or combined together to form a cyclic ring system of a total of 5-6 atoms containing carbon and optionally one or two hetero atoms selected from oxygen, nitrogen or sulfur. The lower alkyl moiety of the lower alkoxy and halogen each have the same meanings as defined above.

In the compounds of general formula **1**, the group R^1 is represented by $-(CH_2)s\text{-}Z\text{-}Ar^1$ group; The representative of such groups may be for example: $-Ar$, $-CH_2Ar^1$, $-(CH_2)_2Ar^1$, $-(CH_2)_3Ar^1$, $-(CH_2)OAr^1$, $-(CH_2)_2OAr^1$, $(-CH_2)_3OAr^1$, $-CH_2\text{-}S\text{-}Ar^1$, $-(CH_2)_2\text{-}S\text{-}Ar^1$, $-(CH_2\text{-}N(R^h)\text{-}Ar^1$, $-(CH_2)_2\text{-}N(Rh)\text{-}Ar^1$ or $-(CH_2)_3\text{-}N(R_b)\text{-}Ar^1$ and the like where Ar^1,Rh & Rb are as defined earlier.

The term " Pharmaceutical acceptable salts" means non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include acetate, ascorbate, benzenesulfonate, benzoate, bicarbonate, borate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, edetate, mesylate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine,

hydrobromide, hydrochloride, hydroxyapthoate, iodide, isothionate, α-ketoglutarate, α-glycerophosphate, glucose-1 phosphate lutarate lactate, lactobionate, laurate, malate, methane-sulphate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, sterate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate. The pharmacological acceptable salts of a compound of the formula **1** possessing an acidic portion is understood to mean the commonplace salts of the compounds of the formula **1** which are formed from non-toxic inorganic or organic bases such as alkali metal, alkaline-earth metal hydroxides like lithium, sodium, potassium, magnesium and calcium hydroxides or amines such as dibenzylethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

It will be appreciated that some of the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in compounds of formula **1** can give rise to stereoisomers and in each case the invention is to be understand to extend to all such stereoisomers, including enantiomers and diastereoisomers and their mixtures, including racemic mixtures. The invention may also contain E & Z geometrical isomers wherever possible in the compounds of general formula **1** which includes the single isomer or mixture of both the isomers.

The invention also envisages within its scope the polymorphs and the analogs of the compounds of the general formula **1** as defined above . Some of the representative compounds according to the present invention are specified below:

1) O-(4-Methoxybenzoyl)-3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl phenyl ketoxime

2) O-(3-Fluorobenzoyl)-3-butoxymethyl-2,3-dihydro benzodioxin-6-yl phenyl ketoxime

3) O-(4-Chloro-3-nitrobenzoyl)-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)phenylket-oxime

4) 3-Ethoxymethyl-6-(3-pyridinyloxy)methyl-2,3-dihydrobenzodioxane hydrochloride

5) O-(3-Nitrobenzoyl)-[3-(benzyloxymethyl)-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

6) O-(4-Chlorobenzoyl)-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-phenyl ketoxime

7) 3-Ethoxy methyl-6-[3,5-dichloro-4-pyridinyloxy]methyl-2,3-dihydro benzodioxane

8) 3-Ethoxymethyl –6-(2,5-dichlorophenoxy)methyl-2,3-dihydro benzodioxane

9) O-(2-Pyridyl)-3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl phenyl ketoxime

10) O-Benzyl-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)phenyl keto oxime

11) N-(2,6-Dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxin-6-carboxamide

12) O-(3-Nitrobenzyl)-3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl phenyl ketoxime

13) O-(3-Chlorobenzyl)-3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl phenyl ketoxime

14) O-(3-Fluorobenzyl)-3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl phenyl ketoxime

15) N-(4-Nitrophenyl)-3-(m-fluorophenoxymethyl)-2,3-dihydrobenzodioxin-6-carboxamide

16) N-(2,5-Dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxin-6-carboxamide

17) N-(4-Fluorophenyl)-3-butoxymethyl-2,3-dihydrobenzodioxin-6-carboxamide

18) O-(4-Nitrobenzyl)-1-(3-ethoxy methyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime

19) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxinyl)-1-hydroxy-2-(3-fluoro phenyl) ethane

20) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(3-fluorophenyl) ethylene

21) N-Cyclopentyl-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

22) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(4-fluorobenzyloxy) methane

23) 1-(3-Butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(4-fluorobenzyloxy) methane

24) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-nitrobenzyloxy) methane

25) O-(4-Nitrobenzyl)-1-(3-ethoxy methyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime

26) O-(4-Trifluoromethylphenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6- yl]phenyl ketoxime

27) O-(4-Isopropylphenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime

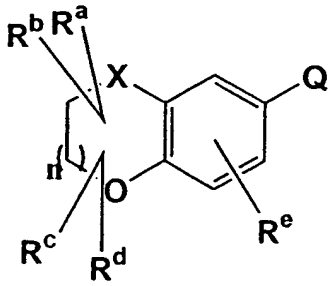
28) O-(2,6-Dichloro-4-pyridylaminocarbonyl)-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

29) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-chlorobenzyloxy) methane

30) 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(2,5-dichlorobenzyloxy) methane

The present invention also relates to a process for the preparation of the novel compound of formula **1.**

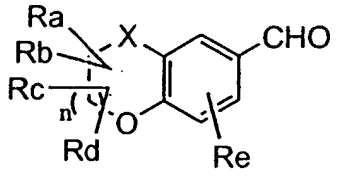
(A) In one embodiment of the present invention there is provided a process for the preparation of compounds of the general formula **1A** ,



1A

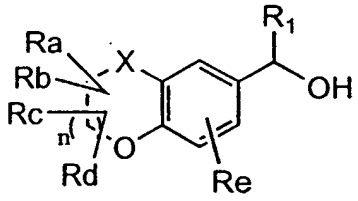
where Q is a group which represents $-C(R^1)=N-O-(Y)_p-W$ wherein Y is substituted or optionally substituted lower alkyl, -C(=O), -C(=S), -C(=O)-O, or C(=O)-NH group; p is an integer of 0 or 1; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups; R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl); and s is zero or the integer 1,2,3,or 4; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, the other symbols having the meanings given earlier which comprises,

(1) reacting the compound of the general formula **9** where X, R^a to R^e have the meanings described above



9

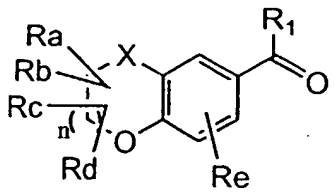
with a group R^1-J where J is halogen other than fluorine and R^1 is a –(CH_2)s-Z-Ar^1 group, where Ar^1 is an hydrogen, optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl, Z is a bond, -O-, -S-, or NR^i and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted loweralkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, in the presence of alkyl lithium or Mg/Li metal and ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxyl compounds of the general formula **10**



10

where R^1 is not a hydrogen and all the other symbols having the meanings given earlier,

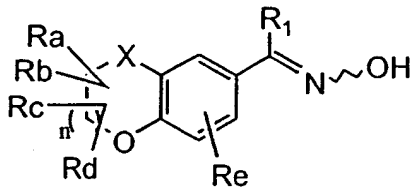
(2) reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



11

where all the symbols have the meanings given earlier

(3) reacting the novel ketone of the formula 11 with hydroxylammonium chloride in the presence of a base and a alcoholic solvent to obtain corresponding novel oxime of the formula 12

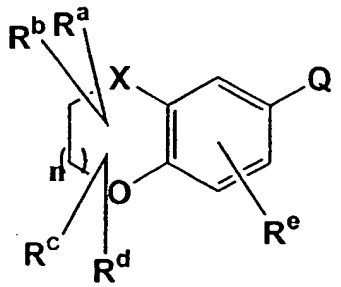


12

(4) reacting the compounds of the formula 12 with a reagent of the formula

W-G-J

where J denotes chlorine or bromine and G represents groups like -CH_2, C(=O), C(=S) -OC(=O) or -NHC(=O) in the presence of a base and aprotic or ethereal solvents to provide the novel compounds of the formula 1A



1A

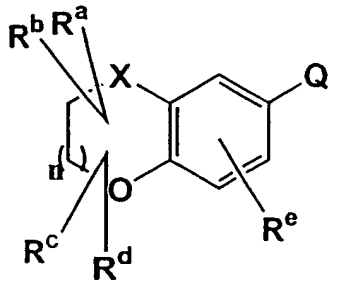
where Q represents -$C(R^1)$=N-O-$(Y)_p$-W where p denotes 0 or 1 and Y represents substituted or unsubstituted lower alkyl, -C(=O) or -C(=S) group,

-C(=O)O group or -C(=O)NH group and X, R^a to R^e, R^1 and W have the meaning described above,

(5) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(6) and if required further purifying the compounds of the formula by conventional methods.

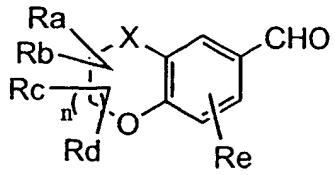
(B) In another embodiment of the present invention there is provided a process for the preparation of the compounds of the formula **1B**



1B

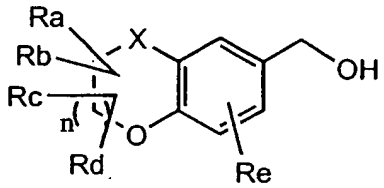
where Q represents **–CH(R^1)-L-W** wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 represents hydrogen, which comprises,

(1) reacting the compound of the formula **9** ,



9

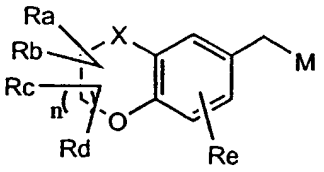
where X, R^a to R^e have the meanings described above, with a reducing agent in the presence of ethereal solvents at a temperature in the range of -10 to 25°C to get the corresponding novel hydroxyl compound of the formula 13,



13

wherein the symbols have the meanings given earlier,

(2) converting the hydroxyl group in the compounds of the formula 13 where R^1 is hydrogen and the other symbols have the meanings described above, into a leaving group M such as halogen, mesylate, tosylate or triflate and the like, by following conventional methods known in literature to obtain the novel compounds of the formula 14,



14

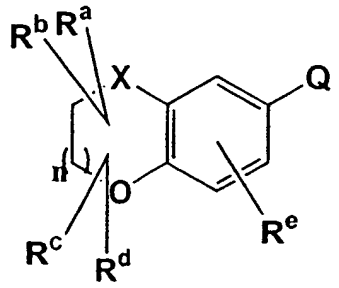
where all the symbols have the meanings given earlier,

(3) reacting the novel compounds of the formula 14 with a reagent of the formula

W-L-H

where L denotes -O, -NR^i, -$S(O)_r$ wherein r represents 0 to 2, and W has the meaning given earlier , in the presence of a base and ethereal or aprotic

solvent at a temperature in the range of 0 to 80 °C to get the novel compounds of the formula **1B**



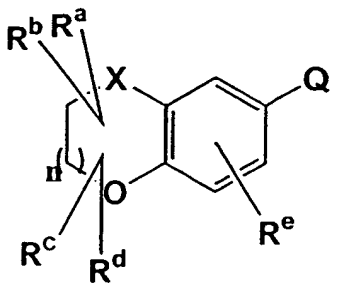
1B

where Q represents **–CH(R^1)-L-W** wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 represents hydrogen, X, R^a to R^e have the meaning described above.

(4) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(5) and if required further purifying the compounds of the formula by conventional methods.

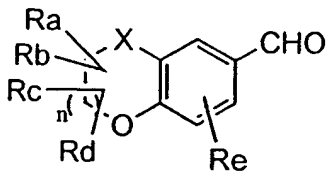
(C) In yet another embodiment of the present invention there is provided a process for the preparation of the compounds of the formula **1C**



1C

where Q represents $-C(R^1)(R^2)-(CHR^j)-W$; wherein W is hydrogen, substituted or unsub-stituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and s is an integer of 0 to 4; R^2 represents hydroxyl, substituted or unsubstituted lower alkoxy, $-OC(=O)-R^k$, $-OC(=O)NHR^k$, in which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; which comprises,

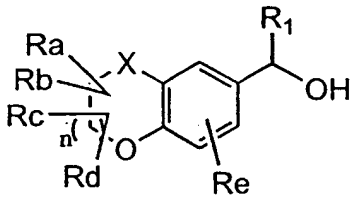
(1) reacting the compound of the formula 9



9

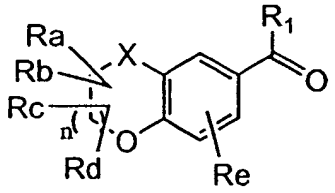
where X, R^a to R^e have the meanings described above with a group R^1-J where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group,

where Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl ; Z is a bond, -O-, -S-, or N(R^i) and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl , substituted or unsubstitued heteroaryl groups, in the presence of alkyl lithium or Mg/Li metal and an ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxy compounds of the general formula **10**



10

where R^1 is not a hydrogen and all the other symbols having the meanings given earlier, reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



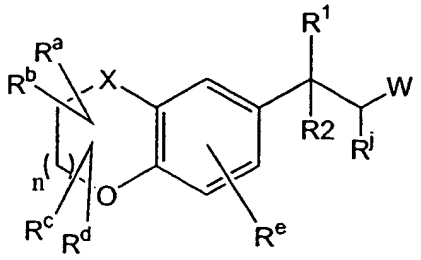
11

where all the symbols have the meanings given earlier,

reacting the novel compounds of the formula **9** or **11** with a reagent

W-(CHR^J)-J

where R^J having the meaning given earlier and J represents halogen other than fluorine, in the presence of magnesium or lithium metal and ethereal or aromatic solvents at a temperature in the range of 0 to 80° C to produce the novel compounds of the formula **15**



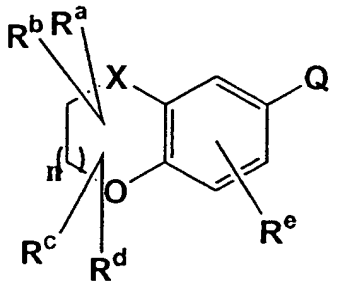
15

where R^a to R^e have the meaning given above and where R^2 represents hydroxyl group and R^j, R^1& W have the meanings given earlier,

(4) reacting the novel compounds of the formula **15** in the presence of a base and a chlorinated solvent with a reagent of the formula

W-G-J

where J denotes chlorine or bromine and G represents groups like -CH_2, C(=O), -OC(=O) or -NHC(=O), to produce the compounds of the formula **1C**



1C

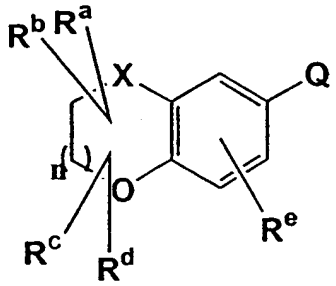
where Q denotes –$C(R^1)(R^2)$-(CHR^j)-W wherein R^2 represents substituted or unsubstituted lower alkoxy, -OC(=O)-R^k, -OC(=O)NHR^k, in which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups ; R^j represents hydrogen, substituted or unsubstitued lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups and X, R^a to R^e, R^1 and W have the meaning described above,

(5) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically

acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(6) and if required further purifying the compounds of the formula by conventional methods.

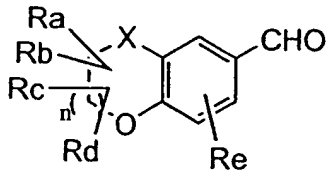
(D) In still yet another embodiment of the present invention there is provided a process for the preparation of the compounds of the formula **1D** ,



1D

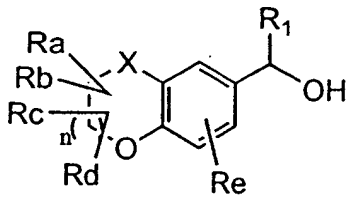
where Q represents $-C(R^1)=C(R^j)-W$ wherein W is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and s is an integer of 0 to 4; R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; which comprises,

(1) reacting the compound of the formula **9**



9

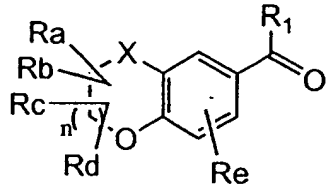
where X, R^a to R^e have the meanings described above with a group $\mathbf{R^1}$-**J** where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group, where Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl ; Z is a bond, -O-, -S-, or $N(R^i)$ and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl , substituted or unsubstitued heteroaryl groups, in the presence of alkyl lithium or Mg/ Li metal and an ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxy compounds of the general formula **10** ,



10

where R^1 and all the other symbols having the meanings given earlier,

(2) reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



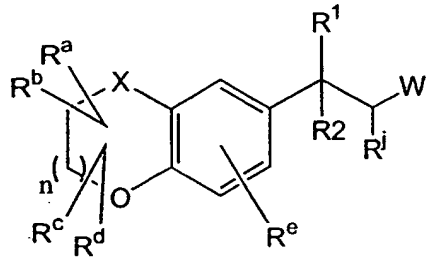
11

where all the symbols have the meanings given earlier,

reacting the novel compounds of the formula 9 or 11 with a reagent

$$W\text{-}(CHR^j)\text{-}J$$

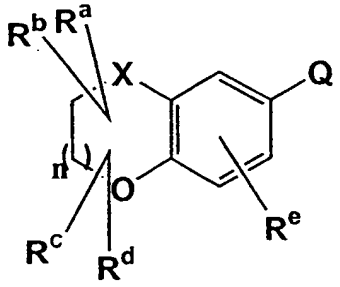
where R^j having the meaning given earlier and J represents halogen other than fluorine, in the presence of magnesium or lithium metal and an ethereal or aromatic solvents at a temperature in the range of 0 to 80° C to produce the novel compounds of the formula 15



15

where R^a to R^e have the meaning given above and where R^2 represents hydroxyl group and R^j, R^1& W have the meanings given earlier,

(5) reacting the novel compounds of the formula 15 with an acid in the presence of ethereal or aromatic solvent to provide the novel compounds of the formula 1D ,



1D

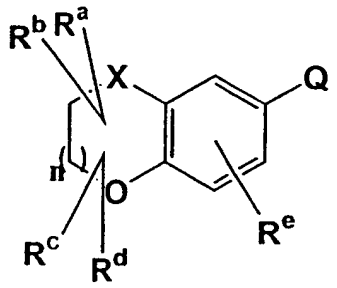
and Q represents $-C(R^1)=C(R^j)-W$ where R^j denotes hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and X, R^a to R^e, R^1 and W have the meaning described above

(6) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically

acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(7) and if required further purifying the compounds of the formula by conventional methods.

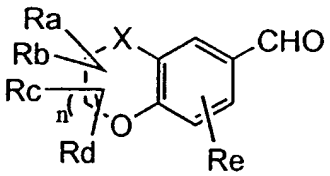
(E) According to one more embodiment of the present invention there is provided a process for the preparation of the general formula **1E,**



1E

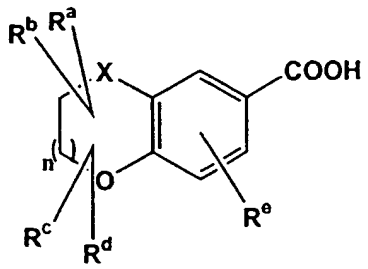
where Q represents a group -CONH-$(CH_2)_t$-Ar^2 where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups, which comprises,

reacting the compounds of the formula **9**



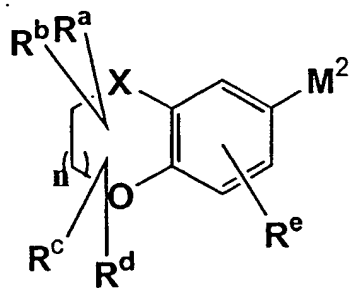
9

where X, R^a to R^e have the meanings described above with a strong oxidizing agent following conventional methods to obtain the novel compounds of the formula **16,**



16

(2) converting the compounds of the formula 16 into the compounds of the formula 17,



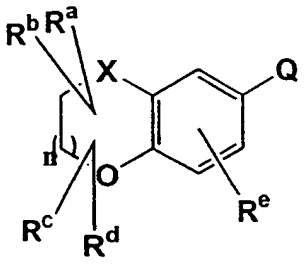
17

where M^2 is an acid chloride or a mixed anhydride such as -CO-O-CO-R^m where R^m denotes lower alkyl groups, by conventional methods,

(3) reacting the novel compounds of the formula 17 with the reagent of the formula

$$Ar^2\text{-}(CH_2)_t\text{-}NH_2$$

where t is 0 to 4 and Ar^2 has the meaning described above, in the presence of a base and ethereal solvent or chlorinated solvent, an aromatic solvent or an aprotic solvent at a temperature in the range of 0 to 80°C to obtain the novel compound of formula 1E,



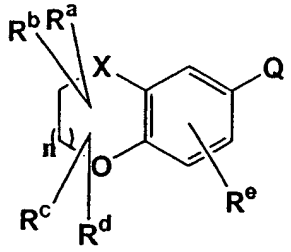
1E

where Q represents a group -CONH-$(CH_2)_t$-Ar^2 where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups and X, R^a to R^e have the meaning described above ;

(4) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(5) .and if required further purifying the compounds of the formula by conventional methods.

(F) According to yet another embodiment of the present invention there is provided a process for the preparation of the compounds of the formula **1F**

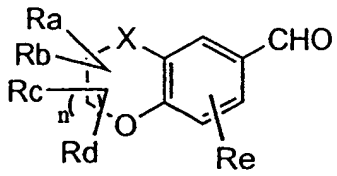


1F

where Q represents **–CH(R^1)-L-W** (wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group –(CH_2)s-Z-Ar^1 wherein Ar^1 is hydrogen, an optionally substituted

monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i , s represents an integer of 0 to 4; which comprises,

(1) reacting the compound of the formula **9** ,

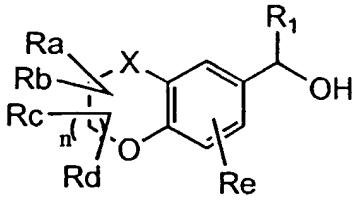


9

where X, R^a to R^e have the meanings described above, with a group

R^1-J

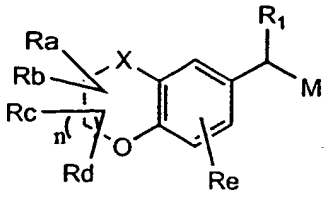
where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group, where Ar^1 is an hydrogen, optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl, Z is a bond, -O-, -S-, or NR^i and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted loweralkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, in the presence of alkyl Lithium or Mg/ Li metal and ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxy compounds of the general formula **10** ,



10

where R^1 and all the other symbols having the meanings given earlier,

(2) optionally converting the hydroxyl group in the compounds of the formula **10** into a group M where M represents amino, thio or sulfonyl group by following conventional methods known in literature to obtain the novel compounds of the formula **18,**



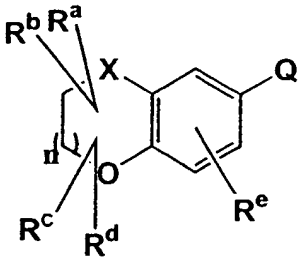
18

where all the symbols have the meanings given earlier,

(3) reacting the novel compounds of the formula **18** with a reagent of the formula

W-J^1

where J^1 is halogen or optionally denotes a leaving group such as mesylate, tosylate or triflate etc., and W has the meaning given earlier , in the presence of a base and an ethereal or aprotic solvent at a temperature in the range of 0 to 80 °C to get the novel compounds of the formula **1F**



1F

where Q represents **–CH(R^1)-L-W** wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group –(CH$_2$)s-Z-Ar^1 wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a

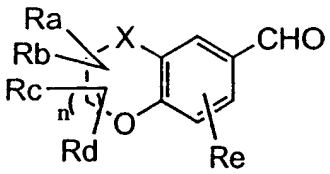
bond, -O-, -S-, or NR^i and s represents an integer of 0 to 4; and X, R^a to R^e have the meaning described above.

(4) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(5) and if required further purifying the compounds of the formula by conventional methods.

The intermediate compounds of the general formulae **10, 11** & **12** prepared in the process of the present invention are also useful as PDE 4 inhibitors as some of these compounds showed good *in vitro* activity against human PDE4 enzyme inhibitory assay.

The starting compounds of the general formula **9**



9

where R^a, R^b, R^c, R^d and R^e have the meaning described above, which are employed in the above processes of the present invention are in general known compounds and may be prepared by the conventional methods reported in the literature.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula **1** are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be

selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontertrachloride and the like. The aromatic solvents which may be employed may be selected from benzene, toluene. The alcoholic solvents which may be employed may be selected from methanol, ethanol, n-propanol, iso propanol, tert.butanol and the like . The aprotic solvents which may be employed may be selected from acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide and the like.

The bases which may be employed in the above processes for the preparation of the compounds of the formula 1 are selected from carbonates such as lithium carbonate, sodium carbonate, potassium carbonate, cesium carbonate; hydride bases such as sodium hydride, potassium hydride; inorganic bases such as potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium tert.amyloxide, sodium methoxide, potassium tert.butoxide, or organic bases such as lithiumdiisopropylamide, lithiumhexmethyldisilazide; alkyl lithium bases such as n-butyl lithium, sec.butyl lithium, tert.butyl lithium and the like.

The acids which may be used in the above processes for the preparation of the compounds of the formula 1 are selected from inorganic acids such as sulfuric acid, hydrochloric acid ; organic acids such as acetic acid, p-tolunesulfonicacid, methanesulfonic acid, trifluoroacetic acid, camphorsulfonic acid; Lewis acids such as borontrifluoride-ether complex and the like.

In general, the reaction time to carry out the above described processes for the preparation of compounds of the formula 1 may be in the range of 0.5 hr to 48 hrs, preferably between 0.5 hr to 16 hrs.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as n-pentane, n-hexane, diethyl ether,

isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, acetonitrile, methanol, ethanol, iso propanol, water or their combinations, or column chromatography using 100-200 mesh silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations. Various polymorphs of a compound of general formula 1 forming part of this invention may be prepared by crystallization of compound of formula 1 under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula 1, as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. Such compositions typically contain from 1 to 20

%, preferably 1 to 10 % by weight of active compound of the formula 1 , the remainder of the composition being pharmaceutically acceptable carriers, diluents or solvents. Suitable pharmaceutically acceptable carriers include solid fillers or diluents and sterile aqueous or organic solutions. The active compounds of the formula 1 will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds of the formula 1 can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula 1 can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds of the formula 1 . The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans. For inhalation, the compounds of the formula 1 can be dispensed through inhaler in the form of drug powder, as well as pharmaceutically acceptable acid addition salts or salts with base or the compounds of the formula 1.

In addition to the compounds of formula 1 the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful anti asthma agents.

The compounds of the formula 1 as defined above may be clinically administered to mammals, including human beings, via either oral or parenteral inhalation routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

The invention is explained in detail in the Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLES

Intermediate 1

Preparation of 3-Ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane

Step 1

To a solution of 3,4-dihydroxy benzaldehyde(50g, 3.62M) in 150mL of N,N-dimethylformamide and potassium carbonate (75g, 1.5equiv.,) a solution of epichloro-hydrine (50g, 1.5equiv.,) dissolved in 150mL of N,N-dimethylformamide was added and the contents were heated to 90°C under N_2 atmosphere with vigorous stirring for 6h. The solvent was removed under vacuum and poured the reaction mixture into ice water. Extracted the aqueous layer with ethyl acetate and washed the organic layer with water, 10% HCl ,brine solution and dried over anh. Sodium sulfate. Concentration of the solvent gave 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane as an oily liquid (58g) which was used as such for the next reaction.

Step-2

To a pre-washed sodium hydride(8.24g,2 equiv., 60% oil dispersion) suspended in N,N-dimethylformamide(60mL) cooled to -10°C, a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane (20g) in N,N-dimethylformamide(40mL) was added slowly over a period of 20min. maintaining the internal temperature below 0°C. Then ethyl bromide(22.43g,2 equiv.,) dissolved in 20 mL of N,N-dimethylformamide was added drop wise to the reaction mixture and the contents were stirred at -10°C for 1.5h. Reaction mixture was quenched with brine and extracted with ethyl acetate. The organic extract was washed thoroughly with water, 5% HCl, brine and dried over anh. sodium sulfate. Removal of solvent produced 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as a thick liquid (22g).

^{1}H NMR ($CDCl_3$, 300MHz) : δ 9.81 (s, 1H), 7.43 (s, 1H), 7.42 (d, J=7.5Hz, 1H), 7.01 (d, J=7.5Hz, 1H), 4.42-4.32 (m, 2H), 4.19 (m, 1H), 3.76-3.64 (m, 2H), 3.62 (q, J=7.2Hz, 2H), 1.23 (t, J=7.0Hz, 3H)

Intermediate 2

Preparation of 3-Butoxymethyl-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3,4-dihydroxy benzaldehyde as described in the step-1 of Intermediate-1.

Step-2

To a pre-washed sodium hydride(4.12g,2 equiv., 60% oil dispersion) suspended in N,N-dimethylformamide(25mL) cooled to -10°C, a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzo-dioxane (10g) in N,N-dimethylformamide(10mL) was added slowly over a period of 20min. maintaining the internal temperature below 0°C. Then n-butyl bromide

(8.47g,2 equiv.,) dissolved in 10 mL of N,N-dimethylformamide was added drop wise to the reaction mixture and the contents were stirred at -10°C for 1.5h. Reaction mixture was quenched with brine and extracted with ethyl acetate. The organic extract was washed thoroughly with water, 5% HCl, brine and dried over anh. sodium sulfate. Removal of solvent produced 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane as a thick liquid (12g).

^{1}H NMR ($CDCl_3$, 300MHz): δ 9.79 (s, 1H), 7.39 (s, 1H), 7.38 (d, J=8.0Hz, 1H), 6.97 (d, J=8.0Hz, 1H), 4.40-4.27 (m, 2H), 4.16 (m, 1H), 3.74-3.69 (dd, J=11Hz, J=4.5Hz, 1H), 3.64-3.59 (dd, J=11Hz, J=6.0Hz, 3.50 (t, J=6.0Hz, 2H), 1.57 (m, 2H), 1.36 (m, 2H), 0.92 (t, J=7.5Hz, 3H).

Intermediate 3

Preparation of 3-(Benzyloxymethyl)-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3,4-dihydroxy benzaldehyde as described in the step-1 of Intermediate-1.

Step-2

To a pre-washed sodium hydride(1.0g,1.5 equiv., 60% oil dispersion) suspended in N,N-dimethylformamide(15mL) cooled to -10°C, a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzo-dioxane (5g, 25.7mM) in N,N-dimethylformamide(15mL) was added slowly over a period of 20min. maintaining the internal temperature below 0°C. Then benzyl bromide(6.5g, 1.5 equiv.,) dissolved in 10 mL of N,N-dimethylformamide was added drop wise to the reaction mixture and the contents were stirred at -10°C for 2h. Reaction mixture was quenched with brine and extracted with ethyl acetate. The organic extract was washed thoroughly with water, 5% HCl, brine and dried over anh. sodium sulfate. Removal of solvent produced 3-(benzyloxymethyl)-6-formyl-2,3-dihydrobenzodioxane as thick liquid (5g).

Intermediate 4

Preparation of 3-(Methanesulfonyloxymethyl)-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3,4-dihydroxybenzaldehyde as described in step 1 of Intermediate 1.

Step 2

To a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane (20.0g, 0.103mol) in dichloromethane (600mL) was added 2 equiv. of triethylamine (20.8mL) followed by 1.5 equiv. of methanesulphonylchloride (17.7gm) at 0°C and the contents were stirred at 0°C for 40min. The reaction was quenched with brine (50mL) and the organic layer was separated and washed with 5%hydrochloric acid, brine and dried over anhydrous sodium sulfate. Removal of solvent produced pale brown viscous residue which was purified by column chromatography using 20% ethyl acetate-chloroform as eluent to give 3-methanesulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane as a off-white solid (13.5g);

mp : 67°C ;

IR (KBr, νmax): 3029, 2939, 2836, 1689, 1605, 1584, 1505, 1443, 1355 , 1281, 1175, 1034, 969, 821, 528 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz) : δ 9.85 (s, 1H), 7.46-7.44(m, 2H), 7.07 (d, J=13.2Hz, 1H), 4.49-4.46 (m, 3H), 4.26-4.17 (qd, J=17Hz, J=9Hz, 2H), 3.12 (s, 3H)

Intermediate 5

Preparation of 3-(N,N-Diethylaminomethyl)-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-methansulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in Intermediate-4.

Step 2

The 3-methanesulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane (25g, 0.091mol) was refluxed in p-xylene (200mL) along with N,N-diethylamine (67.1mL) for 24h. The solvent was distilled off and the residue was purified by column chromatography using 30% ethylacetate-chloroform as eluent to give 3-(N,N-diethylaminomethyl)-6-formyl-2,3-dihydrobenzodioxane as an yellow oil (21g);

IR (neat, ν_{max}): 2969, 2933, 2874, 2816, 2730, 1693, 1605, 1583, 1504, 1441, 1387, 1279, 1206, 1072, 1027, 902, 816, 614 cm^{-1}; 1H NMR ($CDCl_3$, 300MHz): δ 9.79 (s, 1H), 7.39-7.36(m, 2H), 6.98 (d, J=9Hz, 1H), 4.40 (dd, J=11Hz, 2H), 4.34 (m, 1H), 4.09 (qd, J=11.4Hz, J=7.2Hz, 2H), 2.82-2.62 (m, 4H), 1.06 (t, 6H).

Intermediate 6

Preparation of 3-Cyclopropylmethoxymethyl-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3,4-dihydroxybenzaldehyde as described in step1 of Intermediate 1.

Step 2

To a pre-washed sodium hydride (2.26g, 1.5 equiv., 60% oil dispersion) suspended in N,N-dimethylformamide (25mL) cooled to -10°C, a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane (6.0g, 0.0309mol) in N,N-dimethyl formamide (20mL) was added slowly over a period of 20min. maintaining the internal temperature below 0°C. A solution of cyclopropylmethylbromide (8.35g, 2 equiv.,) in N,N-dimethylformamide (20mL) was added dropwise to the reaction mixture and the contents were stirred at 0°C for 2.5h. The reaction was quenched with brine, diluted with water, and extracted with ethyl acetate. The organic extract was washed thoroughly with water, 5%hydrochloric acid, brine and dried over anhydrous sodium sulfate. Evaporation of solvent produced 3-cyclopropylmethoxy-methyl-6-formyl-2,3-dihydrobenzodioxane as a brown viscous liquid (5.2g);

IR (neat, ν_{max}): 3080, 3004, 2872, 2732, 1692, 1583, 1605, 1504, 1442, 1392, 1280, 1111, 1030, 879, 817, 786, 614 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ 9.79 (s, 1H), 7.39 (m, 2H), 6.98(d, J=8.0Hz, 1H), 4.41-4.30 (m, 2H), 4.18 (m, 1H), 3.78-3.74 (dd, J=11Hz, J=4.5Hz, 1H), 3.68-3.63 (dd, J=11Hz, J=6.0Hz, 1H), 3.37 (d, J=7.0Hz, 2H), 1.07 (m, 1H), 0.55 (m, 2H), 0.22 (m, 2H).

Intermediate 7

Preparation of 3-tert.Butyldimethylsilyloxymethyl-6-formyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3,4-dihydroxybenzaldehyde as described in step1 of Intermediate 1.

Step 2

To a pre-washed sodium hydride (.296g, 1.2 equiv., 60% oil dispersion) suspended in THF (10mL) cooled to -10°C, a solution of 3-hydroxymethyl-6-formyl-2,3-dihydrobenzodioxane (1.0g, 0.0052mol) in THF (10mL) was added slowly over a period of 20min. maintaining the internal temperature below 0°C. A solution of tert.butyldimethylsilylchloride (0.93g, 1.2 equiv.,) in THF (5mL) was added dropwise to the reaction mixture and the contents were stirred at 0°C for 1h. The reaction was quenched with brine, diluted with water, and extracted with ethyl acetate. The organic extract was washed thoroughly with water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent produced 3-tert.butyldimethylsilyloxymethyl-6-formyl-2,3-dihydrobenzodioxane as a yellow viscous liquid (1.4g);

IR (neat, νmax): 2953, 2929, 2885, 2857, 1694, 1605, 1584, 1505, 1441, 1325, 1281, 1258, 1138, 1113, 1032, 838, 780 cm-1.; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 9.70 (s, 1H), 7.29 (s, 1H), 7.28 (d, J=8.4Hz, 1H), 6.96 (d, J=8.4Hz, 1H), 4.31 (dd, J=11Hz, J=1.8Hz, 1H), 4.10 (m, 2H), 3.84 (dd, J=11Hz, J=4.5Hz, 1H), 3.73 (dd, J=11Hz, J=6.0Hz, 1H), 0.84 (s, 9H), 0.11 (s, 6H).

EXAMPLE 1

Preparation of 3-Ethoxymethyl-6-(3,5-dichloro-4-pyridinyloxy) methyl-2,3-dihydrobenzodioxane

Step 1

3-Ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (4.8gm,0.021M) dissolved in methanol(50mL) was treated with sodium borohydride (2.04gm,2.5equiv.,) at 0°C and the contents were stirred for 1.5h by allowing the temperature to warm to 25°C. Reaction was quenched with acetone(2mL) and evaporated the solvents to dryness under vacuum.

Diluted the residue with 60mL of ether and extracted the organic layer with water and brine solution and dried over anh. sodium sulfate. Concentration of the solvent provided novel 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane (4.5gm) which was pure enough to carryout the next reaction.

Step 2

A dry diethyl ether(80mL) solution of 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane (4.5gm)obtained from the above reaction was cooled 0°C and continuously bubbled HCl gas until the starting hydroxyl compound disappears. N_2 gas is bubbled through the solution to remove the excess dissolved HCl gas and concentrated the solvent to dryness. Extraction of the residue with pentane and evaporation of the solvent gave novel 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane(3.5gm);

IR(neat, ν_{max}) : 2975, 2813, 1591, 1508, 1439, 1284, 1119, 1038, 814, 691 cm^{-1};

Step 3

A solution of 3,5-dichloropyridin-4-one (280mg, 1.1equiv) dissolved in 20mL of N,N-dimethylformamide was treated with 500mg of potassium carbonate followed by a solution of 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane(500mg) in 5mL of N,N-dimethylformamide. The reaction mixture was heated to 80°C for 2hrs and the poured into water. Extracted the aqueous layer with ethyl acetate and washed the organic layer with water, brine solution and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over column chromatography provided 300mg of 3-ethoxymethyl-6-(3,5-dichloro-4-pyridinyloxy)methyl-2,3-dihydrobenzodioxane as a solid ; mp : 127 °C;

IR(KBr, ν_{max}) : 2975, 1627, 1592, 1510, 1280, 1118, 1031, 879, 822 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.60(s,2H), 6.92(d, J=8Hz, 1H), 6.76(s, 1H), 6.71(d, J=8Hz 1H), 4.85(s,2H), 4.35-4.30(m,2H), 4.09(dd, J=12Hz, J=9Hz,1H), 3.67(qd,J=12Hz,J=6Hz,2H), 3.58(q,J=9Hz,2H), 1.23(t,J=7Hz,3H);

EXAMPLE 2

Preparation of 3-Ethoxymethyl-6-(2,5-dichlorophenoxy) methyl-2,3-dihydrobenzodioxane

Step 1

3-Ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (4.8gm,0.021M) dissolved in diethyl ether(50mL) was treated with lithium aluminium hydride (2.0 gm,.,) at 0°C and the contents were stirred for 1.5h by allowing the temperature to warm to 25°C. Reaction was quenched with acetone(2mL) and evaporated the solvents to dryness under vacuum. Diluted the residue with 60mL of ether and extracted the organic layer with water and brine solution and dried over anhydrous sodium sulfate. Concentration of the solvent provide 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane(4.5gm) which was pure enough to carryout the next reaction.

Step 2

A dry diethyl ether(80mL) solution of 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane (4.5gm)obtained from the above reaction was cooled to 0°C and continuously bubbled HCl gas until the starting hydroxyl compound disappears. N_2 gas is bubbled through the solution to remove the excess dissolved HCl gas and concentrated the solvent to dryness. Extraction of the residue with pentane and evaporation of the solvent gave 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzo-dioxane(3.5gm);

IR(neat, ν_{max}) : 2975, 2813, 1591, 1508, 1439, 1284, 1119, 1038, 814, 691 cm^{-1};

Step 3

A solution of 3,5-dichlorophenol (200mg, 1.1equiv) dissolved in 10mL of N,N-dimethylformamide was treated with 400mg of potassium carbonate followed by a solution of 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane(250mg) in 5mL of N,N-dimethylformamide. The reaction mixture was heated to 80°C until the starting material is disappeared. The reaction mixture was poured into water and extracted with ethyl acetate. Washed the organic layer with water, brine solution and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over column chromatography using 5% ethyl acetate-pet.ether provided 290mg of 3-ethoxymethyl-6-(2,5-dichlorophenoxy)methyl-2,3-dihydrobenzodioxane as solid compound; mp : 58°C ;

IR(KBr, ν_{max}) : 2974, 2931, 2872, 1592, 1574, 1440, 1380, 1260, 1135, 1055, 869, 792 cm^{-1}.

EXAMPLE 3

Preparation of 3-Ethoxymethyl-6-(3-pyridinyloxy) methyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in the step-1 of the Example 1.

Step 2

3-Ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane was prepared from 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane as described in the step-2 of the Example 1.

Step 3

A solution of 3-pyridinol (200mg, 1.1equiv) dissolved in 20mL of N,N-dimethylformamide was treated with 500mg of potassium carbonate followed by a solution of 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane(500mg) in 5mL of N,N-dimethylformamide. The reaction mixture was heated to 80° C for 3hrs and poured into water. Extracted the aqueous layer with ethyl acetate and washed the organic layer with water, brine solution and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue (300mg) over column chromatography using 15% ethyl acetate-chloroform solvent provided 240mg of 3-ethoxymethyl-6-(3-pyridinyloxy)methyl-2,3-dihydrobenzodioxane as solid compound;

IR(KBr, ν_{max}) : 2975, 2920, 2873, 1592, 1574, 1509, 1426, 1278, 1118, 1045, 807, 707 cm^{-1}.

EXAMPLE 4

Preparation of 3-Ethoxymethyl-6-(4-fluorophenyl) thiomethyl-2,3-dihydrobenzodioxane

Step 1

Initially 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in the step-1 of the Example 1.

Step 2

3-Ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane was prepared from 3-ethoxymethyl-6-hydroxymethyl-2,3-dihydrobenzodioxane as described in the step-2 of the Example 1.

Step 3

A solution of p-fluorobenzene thiol (160mg, 1.2equiv) dissolved in 20mL of N,N-dimethylformamide was treated with 560mg of potassium

carbonate followed by a solution of 3-ethoxymethyl-6-chloromethyl-2,3-dihydrobenzodioxane(250mg) in 5mL of N,N-dimethylformamide. The reaction mixture was heated to 80°C for 1.5hrs and poured into water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine solution and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue (300mg) over column chromatography using 20% ethyl acetate-pet.ether solvent gave 210mg of 3-ethoxymethyl-6-(4-fluorophenyl) thiomethyl-2,3-dihydrobenzodioxane;

IR(KBr, ν_{max}) : 2975, 2873, 1590, 1508, 1490, 1438, 1275, 1225, 1118, 1091, 1039, 818, 632 cm^{-1}.

EXAMPLE 5

Preparation of O-(4-Chlorobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime

Step 1

To a freshly dried magnesium turnings (1.3g, 2 equiv.,) suspended in 30mL of dry ether was added a pinch of iodine followed by bromobenzene (8.54g,2 equiv.,) dissolved in 40mL of dry ether and the contents were stirred at room temperature for 1hr so that the magnesium is consumed to form a Grignard reagent. 3-Ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane(6g, 27mM) dissolved in 70mL of dry ether was added to the above solution over a period of 20min. and the reaction mixture was continued to stir for an additional 1hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 6.5g of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol which was subjected to oxidation reaction.;

IR(neat, ν_{max}) : 3411, 1592, 1505, 1274, 1116, 1036, 700 cm^{-1};

Step 2

To a suspended solution of pyridinium chlorochromate(PCC)(5.4g, 4 equiv) in dichloromethane(100mL), 4A° molecular sieves were added followed by a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol (6g) in dichloro-methane (50mL). The reaction mixture was stirred at 25°C for 2h and quenched with dry ether. Decanted the organic layer and passed the solution through a small column of celite pad. The resulting organic layer was concentrated to dryness to obtain (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone (5g);

IR(neat, ν_{max}) : 2975, 1653, 1605, 1580, 1504, 1432, 1318, 1282, 1116, 1032, 734, 709 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz) : δ 7.74 (d, J = 7 Hz, 2H), 7.60 - 7.35 (m,5H), 6.95 (d J = 8Hz,1H), 4.35 - 4.30 (m, 2H), 4.09(dd, J=12Hz, J=9Hz,1H), 3.67(qd, J=12Hz, J=6Hz,2H), 3.58(q, J=9Hz,2H), 1.23(t,J=7Hz,3H);

Step 3

To a solution of (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl) phenyl ketone (4g, 13.37mM) in methanol (100mL), hydroxylammonium chloride (2.32g, 2.5 equiv) was added and heated to reflux for 4hrs in the presence of pyridine (1mL). Methanol was evaporated and the residue was poured into water. Aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anh. sodium sulfate. Concentration of the solvent provided 3.6 gm of (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketoxime as solid.; mp : 68-70 °C ;

IR(KBr, ν_{max}) : 3306,2875, 1581, 1507, 1325, 1272, 1117, 1037, 698 cm^{-1};

Step 4

A solution of (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketoxime (314mg, 1mM) in dichloromethane (20mL) was treated with p-chlorobenzoyl chloride(210mg, 1.2equiv.,) in the presence of pyridine (0.2mL) and the reaction mixture was stirred at room temperature for 1h. T

The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 10% ethyl acetate-pet.ether furnished O-(4-chlorobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime (180mg) as mixture of E & Z isomers;

IR(KBr, ν_{max}) : 2975, 1749, 1592, 1506, 1329, 1274, 1251, 1092, 1074, 752 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.84 (d,J=7Hz,1H),7.68(d, J=8Hz,1H), 7.64(d, J=8Hz,1H), 7.52-7.15(m,7H), 7.0-6.88(m,2H), 4.35-4.30(m,2H), 4.09(dd, J=12Hz, J=9Hz,1H), 3.67(qd, J=12Hz, J=6Hz,2H), 3.58(q,J=9Hz,2H), 1.23(t,J=7Hz,3H) ;

EXAMPLE 6

Preparation of O-(3-Fluorobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5.

Step 4

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (350mg) in dichloromethane (25mL) was treated with m-fluoro benzoylchloride(220mg, 1.2equiv.,) in the presence of pyridine (0.2mL) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 8% ethyl acetate -pet.ether furnished O-(3-fluorobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime (108mg) as mixture of E & Z isomers;

IR(KBr, ν_{max}) : 2928, 1745, 1605, 1507, 1332, 1274, 1250, 1159, 1074, 873, 854, 770, 757, 703 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.72(d, J=7Hz,1H), 7.65(d, J=7Hz,1H), 7.56(d, J=7Hz,1H), 7.52-7.18(m,6H), 6.99(s,1H), 6.97(d, J=8Hz,1H), 6.89(d, J=8Hz,1H), 4.45-4.35(m,2H), 4.18(dd, J=12Hz, J=9Hz,1H), 3.70(qd, J=12Hz, J=6Hz,2H), 3.58(q, J=9Hz,2H), 1.21(t,J=7Hz,3H)

EXAMPLE 7

Preparation of O-(3-Nitrobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxinyl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

To a suspended solution of manganese dioxide (4g,) in acetone(100mL) were added followed by a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol (5g) in acetone(50mL). The reaction mixture was stirred at 25°C until the starting alcohol is consumed. Diluted the contents with acetone and the organic layer was passed through a small column of celite pad. The resulting organic layer was concentrated to dryness to obtain 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone (4g) which is spectroscopically identical to the compound obtained in step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5.

Step 4

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (160mg) in dichloromethane (15mL) was treated with m-nitrobenzoyl chloride(110mg, 1.2equiv.,) in the presence of pyridine (0.2mL) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium

bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 10% ethyl acetate -pet.ether furnished O-(3-nitrobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzo-dioxinyl]phenyl ketoxime (180mg) as mixture of E & Z isomers.;

IR(KBr, ν_{max}) : 1755, 1533, 1505, 1350, 1326, 1242, 1115, 904, 715 cm^{-1} ; ^1H NMR ($CDCl_3$, 300MHz) : δ 8.61(s,1H), 8.41(d, J= 8Hz,1H), 8.32(d, J=8Hz,1H), 7.71-7.62(m,2H), 7.52-7.39(m,3H), 7.08-7.01(m,2H), 6.90(d, J= 8.4Hz,1H), 4.35-4.30(m,2H), 4.09(dd, J=12Hz, J=9Hz,1H), 3.67(qd, J=12Hz, J=6Hz,2H), 3.58(q, J=9Hz,2H), 1.23(t,J=7Hz,3H) ;

EXAMPLE 8

Preparation of O-(4-Fluoro-3-nitrobenzoyl)-[3-ethoxymethyl-2,3-Dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydro-benzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (300mg, 1mM) in dichloromethane (20mL) was treated with 4-

fluoro-3-nitrobenzoyl chloride (213mg, 1.1equiv.,) in the presence of pyridine (0.5mL) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 5% ethyl acetate-chloroform furnished O-(4-fluoro-3-nitrobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin -6-yl]phenyl ketoxime (180mg) as mixture of E & Z isomers.; Spectral data of the less polar isomer : mp :155°C;

IR(KBr, ν_{max}) : 1752, 1619, 1543, 1504, 1351, 1328, 1272, 1252, 1219, 1118,1036, 693 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 8.47(d, J=7Hz,1H), 8.30-8.22(m,1H), 7.72-7.64(m,2H), 7.48(q, J=7Hz,1H), 7.44-7.34(m,3H), 7.04(s, 1H), 7.01(d, J=8Hz,1H), 6.89(d,J=8Hz,1H), 4.45-4.38(m,2H), 4.19(dd, J=12Hz, J=9Hz,1H), 3.72(qd, J=12Hz, J=6Hz,2H), 3.58(q,J=9Hz,2H), 1.22(t,J=7Hz,3H) ; More polar isomer : mp : 121°C ;

EXAMPLE 9

Preparation of O-(3-Carbomethoxy-5-nitrobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (300mg, 1mM) in dichloromethane (15mL) was treated with 3-carbomethoxy-5-nitrobenzoyl chloride (253mg, 1.1equiv.,) in the presence of pyridine (0.5mL) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 5% ethyl acetate-chloroform furnished O-(3-carbomethoxy-5-nitrobenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime (190mg) as mixture of E & Z isomers.; Spectral data of the less polar isomer : mp :146°C;

IR(KBr, ν_{max}): 1759, 1732, 1541, 1506, 1306, 1225, 1119, 924, 724, 708cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 9.01(s, 1H), 8.85(s, 1H), 8.79 (s,1H), 7.75-7.65 (m,2H), 7.53-7.38 (m,3H), 7.07 (d, J = 8Hz,1H), 7.05(s, 1H), 6.94(d, J = 8Hz,1H), 4.50-4.42 (m, 2H), 4.25 (dd, J_1 = 12Hz, J_2 = 9 Hz, 1H), 4.01 (s,3H), 3.70(qd, J_1 = 12Hz, J_2 = 6Hz, 2H), 3.58(q, J=9Hz,2H), 1.21(t, J= 7Hz, 3H); More polar isomer : mp : 136°C ;

EXAMPLE 10

Preparation of O-(4-tert.Butylbenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (300mg, 1mM) in dichloromethane (15mL) was treated with 4-tert.butylbenzoyl chloride (206mg, 1.1equiv.,) in the presence of pyridine (0.2mL) and the reaction mixture was stirred at room temperature for 1h. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 1% ethyl acetate-chloroform furnished O-(4-tert.butylbenzoyl)-[3-ethoxymethyl-2,3-dihydrobenzo dioxin-6-yl]phenyl ketoxime (190mg) as mixture of E & Z isomers.; Careful column

purification also produced the independent isomers. Less polar isomer was isolated as solid (70mg); mp : 116°C;

IR (KBr, ν_{max}) : 2962, 1744, 1610, 1581, 1505, 1331, 1276, 1258, 1112,1081, 700 cm^{-1} ; More polar isomer was also isolated as solid(45mg); mp : 125°C ;

EXAMPLE 11

Preparation of O-(3-Chlorobenzoyl)-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

To a freshly dried magnesium turnings (1.3g, 2 equiv.,) suspended in 30mL of dry ether was added a pinch of iodine followed by bromobenzene (8.54g,2 equiv.,) dissolved in 40mL of dry ether and the contents were stirred at room temperature for 1hr so that the magnesium is consumed. 3-Butoxymethyl-6-formyl-2,3-dihydrobenzodioxane(6g, 27mM) dissolved in 70mL of dry ether was added to the above solution over a period of 20min. and the reaction mixture was continued to stir for an additional 1hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 6.0g of 1-[3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol which was subjected to oxidation reaction.;

IR(neat, ν_{max}) : 3428, 3061, 3029, 2958, 2871, 1592, 1505, 1454, 1435, 1275, 1208, 1118, 1036, 878, 813, 738, 700 , 650 cm^{-1};

Step 2

To a suspended solution of pyridinium chlorochromate(PCC)(5.0g, 4 equiv) in dichloromethane(80mL), 4A° molecular sieves were added followed by a solution of 1-[3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol (5g) in dichloro-methane (50mL). The reaction mixture

was stirred at 25°C for 2h and quenched with dry ether. Decanted the organic layer and passed the solution through a small column of celite pad. The resulting organic layer was concentrated to dryness to obtain (3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone (5g);

IR(neat, ν_{max}) : 3062, 2872, 1651, 1605,1580, 1505, 1433, 1282, 1116, 1033, 734, 708 cm^{-1} ;

Step 3

To a solution of 3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone (4g) in methanol (100mL), hydroxylammonium chloride (2.32g, 2.5 equiv) was added and heated to reflux for 4hrs in the presence of pyridine (1mL). Methanol was evaporated and the residue was poured into water. Aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anh. sodium sulfate. Concentration of the solvent provided 3.5 gm of 3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime as solid ;

IR(KBr, ν_{max}) : 3306, 3062, 2932, 1582, 1506, 1325, 1273, 1118, 1037, 933, 817, 767, 698 cm^{-1} ;

Step 4

A solution of 3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (200mg, 0.58mM) in dichloromethane (25mL) was treated with m-chlorobenzoyl chloride(153mg, 1.5equiv.,) in the presence of pyridine (0.5mL) and the reaction mixture was stirred at room temperature for 45min. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 10% ethyl acetate-pet.ether furnished 150mg of O-(3-chlorobenzoyl)-[3-butoxymethyl-2,3-dihydrobenzodioxin -6-yl]phenyl

ketoxime ; Careful column purification also produced the independent isomers. Less polar isomer was isolated as liquid (80mg); More polar isomer was isolated as solid(40mg); Spectral data of more polar isomer : mp : 94°C ; IR(KBr, ν_{max}) : 3067, 2932, 1752, 1572, 1506, 1329, 1274, 1235, 1118, 1063, 884, 739, 699 cm^{-1}; ^1H NMR(300 MHz,$CDCl_3$): δ 7.71(s,1H), 7.62(d,J=6Hz, 1H), 7.51-7.46(m,4H), 7.38-7.31(m,2H), 7.28-7.25(m,2H), 7.18(s,1H), 6.89(d, J=8Hz,1H), 4.40-4.25(m,2H), 4.18-4.05(m,1H), 3.70-3.58(m,2H), 3.49(t, J= 6Hz, 2H), 1.65-1.52(m,2H), 1.42-1.28(m, 2H), 0.91(t,J=7Hz, 3H) ;

EXAMPLE 12

Preparation of O-(m-Nitrobenzoyl)-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-11.

Step 2

3-Butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 11.

Step 3

3-Butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-11;

Step 4

A solution of 3-butoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (200mg, 0.58mM) in dichloromethane (25mL) was treated with m-nitrobenzoyl chloride(108mg, 1.0equiv.,) in the presence of pyridine

(0.2mL) and the reaction mixture was stirred at room temperature for 45min. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 10% ethyl acetate-pet.ether furnished 180mg of O-(3-nitrorobenzoyl)-[3-butoxymethyl-2,3-dihydrobenzo dioxin-6-yl]phenyl ketoxime ; Spectral data of less polar isomer; mp : 88.6°C ;

IR(KBr, ν_{max}) : 3085, 2933, 1755, 1537, 1505, 1350, 1329, 1242, 1116, 1034, 907, 716 cm^{-1};^{1}H NMR(300MHz,$CDCl_3$): δ 8.60(s,1H), 8.40(d, J=6Hz, 1H), 8.30(d, J=6Hz,1H), 7.72-7.62(m,3H), 7.53-7.36(m,3H), 7.08(s, 1H), 7.04(d, J=8Hz,1H), 6.91(d, J=8Hz,1H), 4.45-4.28(m,2H), 4.22-4.18(m,1H), 3.80-3.62(m,2H), 3.49(t, J= 6Hz, 2H), 1.65-1.52(m,2H), 1.42-1.28(m, 2H), 0.91(t,J=7Hz, 3H) ;

EXAMPLE 13

Preparation of O-(m-Nitrobenzoyl)-1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-2-phenyl ethanone oxime

Step 1

To a freshly dried magnesium turnings (1.3g, 2 equiv.,) suspended in 30mL of dry ether was added a pinch of iodine. Benzylbromide (8.54g,2 equiv.,) dissolved in 40mL of dry ether was then added slowly to the magnesium in such a rate that the reaction was initiated. The addition of the remaining benzyl bromide solution was continued while stirring the contents vigorously until all the magnesium is consumed. 3-Ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane(6g, 27mM) dissolved in 70mL of dry ether was added to the above solution over a period of 20min. and the reaction mixture was continued to stir for an additional 1hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and

extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 6.5g of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-2-phenyl ethanol which was subjected as such to the next reaction.;

IR(neat, ν_{max}) : 3429, 3028, 2874, 1592, 1505, 1275, 1117, 1040, 872, 814, 753, 700 cm^{-1};

Step 2

To a suspended solution of pyridinium chlorochromate(PCC)(5.0g, 4 equiv) in dichloromethane(80mL), 4A° molecular sieves were added followed by a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanol (5g) in dichloro-methane (50mL). The reaction mixture was stirred at 25°C for 2h and quenched with dry ether. Decanted the organic layer and passed the solution through a small column of celite pad. The resulting organic layer was concentrated to dryness to obtain 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone(4.0g);

IR(neat, ν_{max}) : 3062, 3029, 2876, 1674, 1605, 1582, 1505, 1320, 1276, 1119, 1030, 815, 730, 698 cm^{-1} ;

Step 3

To a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone (4g) in methanol (100mL), hydroxylammonium chloride (2.32g, 2.5 equiv) was added and heated to reflux for 4hrs in the presence of pyridine (1mL). Methanol was evaporated and the residue was poured into water. Aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anh. sodium sulfate.

Concentration of the solvent provided 3.2 g of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime as solid.; mp : 56-58 °C;

IR(KBr, ν_{max}) : 3289, 3062, 3029, 2869, 1610, 1583, 1511, 1453, 1310, 1277, 1118, 1058, 1030, 978, 871, 814, 727, 701, 612, 598 cm^{-1} ;

Step 4

A solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime (200mg, 0.58mM) in dichloromethane (25mL) was treated with m-nitrobenzoyl chloride(153mg, 1.5equiv.,) in the presence of pyridine (0.5mL) and the reaction mixture was stirred at room temperature for 45min. The reaction mixture was poured into ice water and extracted with chloroform. The organic layer was washed with water, saturated sodium bicarbonate solution, brine and dried over anh. sodium sulfate. Evaporation of solvent and purification of the residue over silica gel column chromatography using 10% ethyl acetate-pet.ether furnished 150mg of O-(m-nitro benzoyl)-1-[3-ethoxymethyl-2,3-dihydrobenzo dioxin-6-yl]-2-phenyl ethanone oxime as a mixture of E & Z isomers; mp : 87°C ;

IR(KBr, ν_{max}) : 3086, 3028, 2976, 1753, 1573, 1534, 1509,1350, 1319, 1277, 1115, 1044, 886, 715 cm^{-1} ; ^1H NMR(300MHz,$CDCl_3$): δ 8.78(s,1H), 8.42(d, J=6Hz, 1H), 8.28(d, J=6Hz,1H), 7.63(t,J=8Hz,1H), 7.45-7.20(m,7H), 6.90(d, J=8Hz,1H), 4.40-4.33(m,2H), 4.32(s,2H), 4.16-4.05(m,1H), 3.76-3.54(m,4H), 1.22(t, J=8Hz,3H).

EXAMPLE 14

Preparation of O-(4-Nitrobenzyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

To a pre-washed suspension of sodium hydride(100mg,2.0 equiv., 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (250mg) dissolved in 10 mL of tetrahydrofuran. Then a solution of 4-nitrobenzyl bromide (200mg) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 2hrs. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography to get the O-(4-nitrobenzyl)-[3-ethoxymethyl-2,3-dihydro benzodioxin-6-yl]phenylketoxime (190mg) ;

IR (neat, ν_{max}) : 2976, 2873, 1605, 1521, 1506, 1345, 1273, 1117, 1032, 780, 698 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz) : δ 8.20(d, J=8Hz,2H), 7.55-7.30(m.7H), 7.00-6.85(m,3H), 5.24(s,2H), 4.35-4.30(m,2H), 4.09(dd, J_1=12Hz,J_2=9Hz, 1H), 3.67(qd, J_1=12Hz,J_2=6Hz, 2H),3.58(q,J=9Hz,2H),1.23(t, J=7Hz,3H);

EXAMPLE 15

Preparation of O-(4-fluorobenzyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

To a pre-washed suspension of sodium hydride(150mg,2.0equiv., 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 3-ethoxy-methyl-2,3-dihydrobenzodioxanyl phenyl keto oxime (300mg) dissolved in 10 mL of tetrahydrofuran. Then a solution of 4-fluorobenzyl bromide (200mg) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 2hrs. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 8% ethyl acetate-pet.ether to obtain O-(4-fluorobenzyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl keto oxime (250mg).

IR(neat, ν_{max}) : 2976, 2872, 1603, 1508, 1273, 1222, 1118, 1030, 993, 820, 699 cm^{-1};

EXAMPLE 16

Preparation of O-(4-Pyridinyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxinyl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5.

Step 4

To a pre-washed suspension of sodium hydride(100mg, 60%oil dispersion) in N,N-dimethylformamide (5mL) was added a solution of 3-ethoxymethyl-2,3-dihydrobenzo dioxanyl phenyl keto oxime (200mg) dissolved in 10 mL of N,N-dimethylformamide. Then a solution of 4-chloropyridine (300mg) dissolved in 5 mL of N,N-dimethylformamide was added to the reaction mixture and the contents were heated to 70°C for 3hrs. Reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 35% ethyl acetate-pet.ether to get O-(4-pyridinyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime (120mg);

IR(neat, ν_{max}) : 2928, 2874, 1585, 1505, 1494, 1323, 1274, 1202, 1119, 1036, 926, 820, 699 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 8.45 (d, J = 8 Hz, 2H), 7.60(d,J=8Hz,1H), 7.50-6.93(m, 9H), 4.35-4.30(m,2H), 4.09 (dd, J = 12Hz, J = 9Hz,1H), 3.67 (qd, J=12Hz, J=6Hz,2H), 3.58(q,J=9Hz,2H), 1.23(t,J=7Hz,3H).

EXAMPLE 17

Preparation of O-(2-Pyridinyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5

Step 4

To a pre-washed suspension of sodium hydride(200mg, 60%oil dispersion) in N,N-dimethylformamide (10mL) was added a solution of 3-ethoxymethyl-2,3-dihydrobenzo dioxanyl phenyl keto oxime (400mg) dissolved in 10 mL of N,N-dimethylformamide. Then a solution of 2-chloropyridine (450mg) dissolved in 5 mL of N,N-dimethylformamide was added to the reaction mixture and the contents were heated to 70°C for 1.5hrs. Reaction mixture was quenched with water and extracted with ethyl

acetate. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 2.5% ethyl acetate-chloroform to get O-(2-pyridinyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime (240mg);

IR (KBr, ν_{max}) : 2976, 1579, 1506, 1464, 1429, 1329, 1273, 1233, 1118, 937, 776, 698 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 25(d,J=7Hz,1H), 7.78-6.82(m,11H), 4.35-4.30(m,2H), 4.09(dd, J=12Hz, J=9Hz,1H), 3.67(qd, J=12Hz, J=6Hz,2H), 3.58(q,J=9Hz,2H), 1.23(t,J=7Hz,3H) ;

EXAMPLE 18

Preparation of O-(3-Chlorobenzyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5.

Step 4

To a pre-washed suspension of sodium hydride(100mg, 60%oil dispersion) in tetrahydrofuran(3mL) was added a solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl keto oxime (300mg, 1mM) dissolved in 5 mL of tetrahydrofuran.. Then a solution of m-

chlorobenzyl bromide (390mg, 1.90mM) dissolved in 3 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 3hrs. Reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 15% ethyl acetate-pet.ether to get O-(3-chlorobenzyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime as liquid(110mg);

IR (neat, ν_{max}) : 3060, 2927, 1579, 1505, 1430, 1329, 1309, 1272, 1119, 1032, 996, 778, 699 cm^{-1} ;

EXAMPLE 19

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(4-fluorobenzyloxy) methane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

To a pre-washed suspension of sodium hydride(80mg, 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzo dioxan-6-yl]-1-phenyl methanol (300mg, 1mM)) dissolved in 6 mL of tetrahydrofuran. Then a solution of 4-fluorobenzyl bromide (378 mg) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 45min.. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 20% ethyl acetate-pet.ether as eluent to get 1-(3-

ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(4-fluorobenzyloxy) methane (130 mg) as a thick liquid;

IR(neat, ν_{max}) : 3061, 3029, 2976, 2870, 1602, 1592, 1507, 1275, 1223, 1086, 1040, 823, 700 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.39-7.21(m,7H, 7.02(t, J=8Hz, 2H), 6.92(s, 1H), 6.82(brs, 2H), 5.25(s, 1H), 4.48(s, 2H), 4.32-4.25(m,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.65(qd, J_1=12Hz, J_2=6Hz, 2H), 3.56(q, J=9Hz,2H),1.22(t, J=7Hz, 3H);

EXAMPLE 20

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-carbomethoxybenzyloxy) methane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

To a pre-washed suspension of sodium hydride(60mg, 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzo dioxan-6-yl]-1-phenyl methanol (300mg) dissolved in 6 mL of tetrahydrofuran. Then a solution of 3-carboethoxy-benzyl bromide (366 mg, 1.5 equiv.,) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 45min.. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 15% acetone-pet.ether as eluent to get 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-carbomethoxybenzyloxy) methane (160mg) as a thick liquid;

IR(neat, ν_{max}) : 3062, 3029, 2976, 2870, 1717, 1591, 1505, 1278, 1197, 1106, 749 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz) : δ 8.00(s,1H),7.95(d, J=7Hz,1H), 7.58(d, J=7Hz,1H), 7.45-7.23(m,6H), 6.94(s, 1H), 6.85(brs, 2H), 5.28(s, 1H), 4.56 (s, 2H), 4.37(q, J= 8Hz,2H), 4.32-4.25(m,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.65(qd, J_1=12Hz, J_2=6Hz, 2H), 3.56(q, J=9Hz,2H), 1.38(t, J=8Hz,3H), 1.22(t, J= 8Hz, 3H);

EXAMPLE 21

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-nitrobenzyloxy) methane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

To a pre-washed suspension of sodium hydride(80mg, 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzo dioxan-6-yl]-1-phenyl methanol (300mg, 1mM)) dissolved in 6 mL of tetrahydrofuran. Then a solution of 3-nitrobenzyl bromide (378 mg) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 45min.. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 20% ethyl acetate-pet.ether as eluent to get 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-nitrobenzyloxy)methane(130mg) as a thick liquid;

IR(neat, ν_{max}) : 3062, 3028, 2871, 1591, 1529, 1506, 1350, 1276, 1116, 1094, 804, 732, 700 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ

8.19(s,1H),8.16(d, J=7Hz,1H), 7.72(d, J=7Hz,1H), 7.52(t, J=7Hz,1H), 7.36-7.22(m,5H), 6.88(s, 1H), 6.79(brs, 2H), 5.38(s, 1H),4.60(s,2H),4.32-4.25(m,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.65(qd, J_1=12Hz, J_2=6Hz, 2H), 3.56(q, J=9Hz,2H), 1.38(t, J=8Hz,3H), 1.22(t, J= 8Hz, 3H);

EXAMPLE 22

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(2,5-dichlorobenzyloxy) methane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

To a pre-washed suspension of sodium hydride(90mg, 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzo dioxan-6-yl]-1-phenyl methanol (250mg, 0.8mM)) dissolved in 5 mL of tetrahydrofuran. Then a solution of 2,5-dichlorobenzyl bromide (378 mg) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 45min. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 20% ethyl acetate-pet.ether as eluent to get 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(2,5-dichloro-benzyloxy) methane (120mg) as a thick liquid;

IR(neat, ν_{max}) : 3063, 3029, 2871, 1591, 1505, 1466, 1453, 1276, 1207, 1097,1042, 878,812, 741, 700 cm-1 ; ^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.60 (s, 1H), 7.40-7.16 (m, 7H), 6.93 (s, 1H), 6.85 (m, 2H), 5.40 (s, 1H),

4.60 (s, 2H), 4.35 (m, 2H), 4.15 (m, 1H), 3.70 (m, 2H), 3.58 (q, J=7.0Hz, 2H), 1.07 (t, J=7.0Hz, 3H).

EXAMPLE 23

Preparation of O-(4-Nitrobenzyl)-1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-2-phenyl ethanone oxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-2-phenyl ethanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-13.

Step 2

1-(3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-2-phenyl ethanol as described in the step-2 of Example 13.

Step 3

1-(3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime was prepared from 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone as described in step-3 of the Example-13.

Step 4

To a pre-washed suspension of sodium hydride(50mg,2.0 equiv., 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethanone oxime (200mg, 0.6mM) dissolved in 10 mL of tetrahydrofuran. Then a solution of 4-nitrobenzyl bromide (200mg, 0.9mM) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 30min. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 12%ethyl acetate-pet.ether to get O-(4-

nitrobenzyl)-1-(3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)-2-phenyl ethan-one oxime (170mg) as thick liquid ;

IR (neat, ν_{max}): 3062, 3028, 2928, 1604, 1573, 1521, 1496, 1453, 1345, 1274, 1119, 1043, 872, 860 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 8.16(d, J=8Hz,2H), 7.40(d, J=8Hz,2H), 7.28-7.10(m,7H), 6.90(d, J=7Hz,1H), 5.28(s, 2H), 4.32-4.25(m,2H), 4.14(s,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.65(qd, J_1=12Hz, J_2=6Hz, 2H), 3.56(q, J=9Hz,2H), 1.21(t, J= 8Hz, 3H);

EXAMPLE 24

Preparation of O-(4-Chloro-3-nitrobenzyl)-[3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime

Step 1

To a freshly dried magnesium turnings (573mg, 1.5 equiv.,) suspended in 30mL of dry ether was added a pinch of iodine followed by bromo-benzene (3.75g,1.5 equiv.,) dissolved in 40mL of dry ether and the contents were stirred under N_2 atmosphere at room temperature until all the magnesium is consumed. 3-Benzyloxymethyl-6-formyl-2,3-dihydro-benzodioxane (5g,15.9mM) dissolved in 70mL of dry ether was added to the above solution over a period of 20min. and the reaction mixture was continued to stir for an additional 2hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 4.8g of 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol;

IR(neat, ν_{max}) : 3428, 3062, 3030, 2870,1592, 1505, 1454, 1275, 1096, 1036, 877, 813, 739, 699 cm^{-1};

Step 2

To a suspended solution of pyridinium chlorochromate(PCC)(3.8g, 1.5 equiv) in dichloromethane(20mL), 4A° molecular sieves were added followed by a solution of 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol (4.0g) in dichloro-methane (20mL). The reaction mixture was stirred at 25°C for 1h and quenched with dry ether. Decanted the organic layer and passed the solution through a small column of celite pad. The resulting organic layer was concentrated to dryness to obtain (3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone (3.5g);

IR(neat, ν_{max}) : 3061, 3030, 2869, 1651, 1605, 1580, 1504, 1432, 1282, 1206, 1107, 1029, 893, 735, 698 cm^{-1} ;

Step 3

To a solution of (3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone (3.5g) in methanol (15mL), hydroxylammonium chloride (1.62g, 2.5 equiv) was added and heated to reflux for 4hrs in the presence of pyridine (0.5mL). Methanol was evaporated and the residue was poured into water. Aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over silica gel column using 12% ethyl acetate-pet.ether provided 2.9g of 3-benzyloxy-methyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime as solid.; mp : 110-113 °C ;

IR(KBr, ν_{max}) : 3230, 3031, 2866, 1610, 1580, 1508, 1454, 1331, 1308, 1272, 1241, 1117, 1106, 1077, 1000, 880, 861, 773, 742, 696,cm^{-1} ;

Step 4

To a pre-washed suspension of sodium hydride(60mg,2.0 equiv., 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime(300mg,

0.83mM) dissolved in 10 mL of tetra-hydrofuran. Then a solution of 4-chloro-3-nitrobenzyl bromide(415mg, 2equiv.,) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 1h. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 10%ethyl acetate-pet.ether to furnish O-(4-chloro-3-nitrobenzyl)-[3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime (140mg) as mixture of E & Z isomers.;

IR(KBr, ν_{max}) : 3062, 3031, 2925, 1611,1536,1505, 1353, 1331, 1273, 1113, 1029, 818, 738, 698 cm^{-1} ;

EXAMPLE 25

Preparation of O-(3-Nitrobenzyl)-1-[3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl] phenyl ketoxime

Step 1

Initially 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-benzyloxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-24.

Step 2

(3-Benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl) phenyl ketone was prepared from 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 24.

Step 3

(3-Benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone oxime was prepared from (3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone as described in step-3 of the Example-24.

Step 4

To a pre-washed suspension of sodium hydride (55mg,2.0 equiv., 60% oil dispersion) in tetrahydrofuran(5mL) was added a solution of 3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime(250mg, 0.69mM) dissolved in 10 mL of tetra-hydrofuran. Then a solution of 3-nitrobenzyl bromide(224mg,1.5 equiv.,) dissolved in 5 mL of tetrahydrofuran was added to the reaction mixture and the contents were heated to reflux for 45min. Reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried. Evaporation of solvent provided the residue which was purified over column chromatography using 12%ethyl acetate-pet.ether to furnish O-(3-nitrobenzyl)-[3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime (120mg) as mixture of E & Z isomers.;

IR(KBr, ν_{max}) : 3062, 3031, 2925, 1612,1581,1529,1505, 1444, 1429,1349, 1329, 1272, 1095, 1029, 894,817, 732, 697 cm^{-1} ;

EXAMPLE 26

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-2-(4-fluorophenyl) ethane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

To a freshly dried magnesium turnings (300mg, 2 equiv.,) suspended in 10mL of dry ether was added a pinch of iodine followed by 3-

fluorobenzyl bromide (1.50g,2 equiv.,) dissolved in 10mL of dry ether over a period of 10min. and the contents were stirred at room temperature for 0.5hr so that the magnesium is consumed to form a Grignard reagent. 3-Ethoxymethyl-2,3-dihydrobenzodioxanyl phenyl ketone (1g) dissolved in 10mL of dry ether was added to the above solution over a period of 10min. and the reaction mixture was continued to stir for an additional 1hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 0.9g of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxinyl)-1-hydroxy-2-(3-fluoro phenyl) ethane as thick liquid.

IR(neat, ν_{max}) : 3363, 3061, 3030, 2926, 1612, 1590, 1505, 1443, 1275,1096, 1035, 876, 746 cm^{-1}.

Example 27

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-nitrobenzoyloxy)-2-(3-fluorophenyl) ethane

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane as described in step-1 of the Example-5.

Step 2

(3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl) ethane was prepared from (3-ethoxymethyl-2,3-

dihydrobenzodioxan-6-yl) phenyl ketone as described in the step-3 of Example 26.

Step 4

A solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl) ethane (100mg) in dichloromethane (10mL) was treated with m-nitrobenzoyl chloride (0.1mL) in the presence of pyridine(0.1mL) and stirred for 1hr. Reaction was quenched with water and diluted with ether. The organic layer was washed with water , sodium bicarbonate solution, brine and dried. Evaporation of solvent afforded 75mg of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-(3-nitrobenzoyloxy)-2-(3-fluorophenyl) ethane.

EXAMPLE 28

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(3-fluorophenyl) ethylene

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane as described in step-1 of the Example-5.

Step 2

(3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl) ethane was prepared from (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl) phenyl ketone as described in step-3 of Example 26.

Step 4

A solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxinyl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl)ethane (100mg) in 10mL of benzene was treated with catalytic amount of p-toluenesulfonic acid and the contents were heated to reflux for 30min. Reaction was quenched with sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was washed with water, brine and dried. Concentration of the solvent and purification of the residue over column chromatography using 5% ethyl acetate-pet.ether as eluent afforded a thick liquid of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(3-fluoro phenyl) ethylene (70mg) as a mixture of E & Z isomers.;

IR(neat, ν_{max}) : 3056, 3021, 2926, 1606, 1580, 1505, 1445, 1274, 1118, 1038, 880. 815, 782, 755, 700 cm^{-1}.

EXAMPLE 29

Preparation of 1-(3-Benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(3-fluorophenyl) ethylene

Step 1

Initially 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-benzyloxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-24.

Step 2

(3-Benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl) phenyl ketone was prepared from 1-[3-benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 24.

Step 3

To a freshly dried magnesium turnings (300mg, 2 equiv.,) suspended in 10mL of dry ether was added a pinch of iodine followed by 3-fluorobenzyl bromide (1.50g,2 equiv.,) dissolved in 10mL of dry ether over

a period of 10min. and the contents were stirred at room temperature for 0.5hr so that the magnesium is consumed to form a Grignard reagent. (3-Benzyloxymethyl-2,3-dihydrobenzodioxan-6-yl)phenyl ketone (1g) dissolved in 10mL of dry ether was added to the above solution over a period of 10min. and the reaction mixture was continued to stir for an additional 1hr at 25°C. Reaction mixture was quenched with saturated ammonium chloride solution and extracted the contents with ether. Organic layer was washed with water , brine and dried over anh. sodium sulfate. Evaporation of solvent afforded 0.9g of 1-(3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl) ethane as thick liquid.

IR(neat, ν_{max}) : 3563, 3061, 3030, 2926, 1614, 1588, 1505, 1447, 1275, 1252, 1096, 1037, 876, 746 699 cm^{-1};

Step 4

A solution of 1-(3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-1-hydroxy-2-(3-fluorophenyl) ethane (100mg) in 10mL of benzene was treated with catalytic amount of p-toluenesulfonic acid and the contents were heated to reflux for 30min. Reaction was quenched with sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was washed with water, brine and dried. Concentration of the solvent and purification of the residue over column chromatography using 5% ethyl acetate-pet.ether as eluent afforded a thick liquid of 1-(3-benzyloxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(3-fluorophenyl) ethylene (70mg) as a mixture of E & Z isomers.;

IR(neat, ν_{max}) : 3060, 3030, 2868, 1606, 1579, 1505, 1444, 1276, 1149, 1097, 1037, 878, 782,750, 699 cm^{-1} ;

EXAMPLE 30

Preparation of N-(4-Methoxyphenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

To a solution of 3-ethoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane(5g, 22.5mM) in 180mL of acetone was added potassium permanganate (7.10g,2equiv.,) and stirred at room temperature for 16hrs. At the end, acetone was removed and diluted with 1% sodium hydroxide solution. The aqueous layer was extracted with ether and separated the layers. The aqueous extract thus obtained was acidified with hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of the solvent provided the 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (2.5g); mp :122-124°C ;

IR (KBr, ν_{max}): 3300, 2975, 1683, 1612, 1585, 1510, 1444, 1422, 1279,1122, 1031, 764, 642 cm^{-1} ;

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid(500mg) in dichloromethane(10mL) was cooled to 0°C and added 1mL of N,N-dimethylformamide. Then oxalyl chloride (0.8mL) was added to the reaction mixture and stirred at room temperature for 16hrs. The solvents were removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 4-methoxy aniline(156mg, 1.26mM) and diisopropylethyl-amine (0.5mL) dissolved in 5mL of 1,2-dichloromethane, a solution of acid chloride (300mg, 1.26mM,obtained from the above step-2) in 5mL of dichloromethane was added and stirred at room temperature for 16hr. The

reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5 % HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 3.5% ethyl acetate-chloroform as eluent has provided N-(4-methoxy phenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (160mg) as solid; mp :103-104 °C;

IR(KBr, ν_{max}) : 3309,3128, 3047, 2975, 1643, 1613, 1542,1584, 1512, 1411,1322, 1282, 1243,1116, 1034, 822, 755, 540, 521 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : d 7.60(br s, 1H), 7.50(d, 8Hz,2H), 7.43(s, 1H), 7.37(d, J=8Hz,1H), 6.95(d, J=8Hz,1H), 6.89(d, J=8Hz,2H), 4.40-4.32(m,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.80(s, 3H), 3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.58(q, J=9Hz,2H), 1.21(t, J= 8Hz, 3H).

EXAMPLE 31

Preparation of N-(2,5-Dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (2g, 8.4mM) in freshly distilled thionyl chloride (20mL) was heated to reflux temperature for 1.5h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 2,5-dichloroaniline (1.63g, 1.2equiv.,) and diisopropylethyl amine (2mL,2.5 equiv.,) dissolved in 10mL of

tetrahydrofuran, a solution of acid chloride (2g, obtained from the above step-2) in 10mL of tetrahydrofuran was added and stirred at room temperature for 16h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, 5%HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 5 % ethyl acetate-pet.ether has provided N-(2,5-dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzo dioxinyl-6-carboxamide(1.40g); mp : 89-90°C;

IR (KBr, ν_{max}) : 3286, 2969, 2873, 1650, 1613, 1578, 1503, 1460, 1406, 1317, 1283, 1107, 1050, 820, 800 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 8.65(s;1H), 8.32(brs, 1H), 7.48(s, 1H), 7.43(d, J=8Hz,1H), 7.33(d, J=8Hz,1H), 7.05(d, J=8Hz,1H), 6.95(d, J=8Hz,1H), 4.45-4.32(m,2H), 4.14(dd, J_1=12Hz, J_2=9Hz,1H), 3.70(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.62(q, J=9Hz,2H), 1.24(t, J= 8Hz, 3H);

EXAMPLE 32

Preparation of N-(2,6-Dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (500mg) in dichloromethane(10mL) was cooled to 0°C and added 1mL of N,N-dimethylformamide. Then oxalyl chloride (0.8mL) was added to the reaction mixture and stirred at room temperature for 16hrs. The solvents were removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 2,6-dichloroaniline (200mg, 1equiv.,) and triethyl amine (0.5mL) dissolved in 6mL of tetrahydrofuran a solution of acid chloride (300mg, 1.26mM,obtained from the above step-2) in 5mL of tetrahydrofuran was added and stirred at room temperature for 16h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5%HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 10 % ethyl acetate-pet.ether has provided N-(2,6-dichlorophenyl)-3-ethoxymethyl-2,3-dihydrobenzo dioxinyl-6-carboxamide (110mg); mp. : 120°C ;

IR(KBr, ν_{max}) : 3237, 2974, 2884, 1645, 1610, 1586, 1495, 1439, 1320, 1280,1200,1133,1115, 1099, 1028, 818, 772, 763 cm^{-1} ;

EXAMPLE 33

Preparation of N-(4-trifluoromethylphenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid(300mg, 1.26mM) in freshly distilled thionyl chloride (5mL)was heated to reflux temperature for 1.5h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 4-trifluoromethylaniline (400mg, 1equiv.,) and diisopropylethyl amine (0.5mL) dissolved in 10mL of tetrahydrofuran, a solution of acid chloride (300mg, obtained from the above step-2) in 5 mL of tetrahydrofuran was added and stirred at room temperature for 16h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water , sodium bicarbonate and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 3.5% ethyl acetate-chloroform has provided N-(4-trifluoromethylphenyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (150 mg) ;mp : 153°C ;

IR(KBr, ν_{max}) : 3346, 2983, 2877, 1654, 1615, 1586, 1525, 1507,1405, 1327, 1286,1163,1124, 1070, 833, 821, 757 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.82(br s, 1H), 7.75(d, 8Hz,2H), 7.62(d, J=8Hz,2H),7.46(s, 1H),7.39(d, J=8Hz,1H), 6.86(d, J=8Hz,1H), 4.43-4.32(m,2H), 4.14(dd, J_1=12Hz, J_2=9Hz,1H), 3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.60(q, J=9Hz,2H), 1.24(t, J= 8Hz, 3H).

EXAMPLE 34

Preparation of N-(6-Methyl-2-pyridinyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid(450mg, 1.66mM) in freshly distilled thionyl chloride (5mL)was heated to reflux temperature for 1.5h. The excess thionyl chloride was removed

under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 2-amino-6-picoline (250mg, 1equiv.,) and trilethyl amine (0.3mL) dissolved in 5mL of tertahydrofuran, a solution of acid chloride (400mg, obtained from the above step-2) in 6 mL of tetrahydrofuran was added and stirred at room temperature for 18h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5% HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 8% acetone-pet.ether has provided N-(6-methyl-2-pyridinyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carbox- amide (120mg); mp : 84-86°C;

IR(KBr, ν_{max}): 3436, 2976, 2882, 1671, 1599, 1584, 1532, 1500, 1454,1391,1283,1193,1122,1023,791,752 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz): δ 8.50 (br s, 1H), 8.17(d, 8Hz,1H), 7.63(t,J=7Hz,1H), 7.53(s,1H), 7.44(d, J=8Hz,1H), 6.95(d, J=8Hz,1H),6.91(d, J=8Hz,1H),4.40-4.32(m,2H), 4.14(dd, J_1=12Hz, J_2=9Hz,1H),3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.58(q, J=9Hz,2H), 2.45(s, 3H),1.24(t, J= 8Hz, 3H);

EXAMPLE 35

Preparation of N-Benzyl-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid(400mg, 1.56mM) in freshly distilled thionyl chloride (5mL)was heated to reflux temperature for 1.5h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of benzylamine (154mg, 1.2equiv.,) and diisopropylethyl amine (0.5mL) dissolved in 5mL of tetrahydrofuran, a solution of acid chloride (300mg, obtained from the above step-2) in 4mL of tetrahydrofuran was added and stirred at room temperature for 16h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water , sodium bicarbonate and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 25%ethyl acetate-pet.ether has provided N-benzyl-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (130mg); mp : 94-96°C ;

IR(KBr, ν_{max}) : 3347, 2976, 2902, 1633, 1612, 1547, 1504, 1321, 1281, 1114, 1093, 1030, 863, 823,755, 699, 658 cm^{-1} ; ^1H NMR($CDCl_3$, 300MHz) : δ 7.38-7.36(m,6H,), 7.30(d, J=8Hz,1H), 6.89(d, J=8Hz,1H), 6.25(BRS, 1h), 4.62(d, J=3Hz,2H), 4.38-4.28(m,2H), 4.10(dd, J_1=12Hz, J_2=9Hz,1H), 3.65(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.55(q, J=9Hz,2H), 1.21(t, J= 8Hz, 3H);

EXAMPLE 36

Preparation of N-Cyclopentyl-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (300mg) in benzene(10mL) was added freshly distilled thionyl chloride (5mL) and the reaction mixture was heated to reflux temperature for 6hrs. The solvents and the excess thionyl chloride were removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of cyclopentyl amine (110mg, 1.0equiv.,) and diisopropylethyl amine (0.5mL) dissolved in 5mL of tetrahydrofuran, a solution of acid chloride (300mg, 1.26mM, obtained from the above step-2) in 4mL of tetrahydrofuran was added and stirred at room temperature for 16h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, sodium bicarbonate and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 20%ethyl acetate-pet.ether has provided N-cyclopentyl-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (135mg); mp : 100-101°C;

IR(KBr, ν_{max}) : 3291, 2955, 2871, 1630, 1604, 1583,1541, 1504, 1321, 1279, 1125, 1085, 1042, 874, 819,769, 702, 549 cm^{-1} .

EXAMPLE 37

Preparation of N-(4-Fluorophenyl)-3-butoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

To a solution of 3-butoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane(5g, 20 mM) in 150mL of acetone was added potassium permanganate (7g,2equiv.,) and stirred at room temperature under nitrogen atmosphere for 16hrs. At the end, acetone was removed and diluted with 1% sodium hydroxide solution. The aqueous layer was extracted with ether and separated the layers. The aqueous extract thus obtained was acidified with hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of the solvent provided the 3-butoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (4.5g) as solid ; mp : 95 °C;

Step 2

A solution of 3-butoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid(350mg) in freshly distilled thionyl chloride (5mL) was heated to reflux temperature for 1.5hr. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 4-fluorophenyl aniline (147mg, 1.2 equiv.,) and N,N-diisopropylethyl amine (0.5mL, 1.5 equiv.,) dissolved in 5mL of tetrahydrofuran, a solution of above acid chloride (300mg) in 5mL of tetrahydrofuran was added and stirred at room temperature for 16hr. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, 5% HCl and brine solution. Concentration of the solvent followed by purification of the residue over

column chromatography using 20% ethyl acetate-pet.ether provided N-(4-fluorophenyl)-3-butoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (150mg) as solid; mp: 110 °C ;

IR(KBr, ν_{max}) : 3344, 2931, 2874, 1649, 1604, 1516, 1402, 1330, 1285, 1224, 1131, 822 cm^{-1};

^1H NMR($CDCl_3$, 300MHz) : δ 7.56(dd,J_1=9Hz,J_2=5Hz, 2H), 7.42(s,1H), 7.36(d, J=8Hz,1H), 7.03(t, J=9Hz,2H), 6.95(d, J=8Hz,1H), 4.40-4.32(m,2H), 4.14(dd, J_1=12Hz, J_2=9Hz,1H), 3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.52(t, J=7Hz,2H),1.64-1.53(m,2H), 1.44-1.32(m,2H), 0.95(t, J= 8Hz, 3H);

EXAMPLE 38

Preparation of N-(2,5-Dichlorophenyl)-3-(m-fluorobenzyloxymethyl)-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

To a solution of 3-(m-fluorobenzyloxymethyl)-6-formyl-2,3-dihydrobenzo dioxane(5g,16mM) in 200mL of acetone was added potassium permanganate (7g,2equiv.,) and stirred at room temperature under nitrogen atmosphere for 16hrs. At the end, acetone was removed and diluted with 1% sodium hydroxide solution. The aqueous layer was extracted with ether and separated the layers. The aqueous extract thus obtained was acidified with hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of the solvent provided the 3-(m-fluorobenzyloxymethyl)-2,3-dihydrobenzodioxan-6-carboxylic acid (2.5g) as solid ; mp : 126-128 °C ;

Step 2

A solution of 3-(m-fluorobenzyloxymethyl)-2,3-dihydrobenzodioxan-6-carboxylic acid(450mg) in freshly distilled thionyl chloride (10mL) was heated to reflux temperature for 1.5hr. The excess thionyl chloride was

removed under reduced pressure to get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 2,5-dichloroaniline (243mg, 1.2 equiv.,) and N,N-diiso-propylethyl amine (0.5mL) dissolved in 10mL of tetrahydrofuran, a solution of acid chloride (400mg, obtained from the above step-2) in tetrahydrofuran(5mL) was added and stirred at room temperature for 16hr. The reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with water, 5% HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 8% acetone-pet.ether has provided N-(2,5-dichlorophenyl)-3-(m-fluorobenzyloxymethyl)-2,3-dihydrobenzodioxinyl-6-carbox-amide (150mg);

IR(KBr, ν_{max}) : 3390,3272, 3102, 2925, 1646, 1612, 1582, 1503, 1407, 1293, 1265, 1191, 1091, 1046, 915, 810 ,749 cm^{-1}.

EXAMPLE 39

Preparation of N-(4-pyridyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-carboxylic acid (350 mg) in benzene(5mL) was added freshly distilled thionyl chloride (5mL) and the reaction mixture was heated to reflux temperature for 6hrs. The solvents and the excess thionyl chloride were removed under vacuum to

get the corresponding acid chloride which was subjected to next reaction as such.

Step 3

To a solution of 4-aminopyridine (141mg, 1.2equiv.,) and triethyl amine (0.5mL) dissolved in 10mL of dichloromethane, a solution of acid chloride (300mg, obtained from the above step-2) in dichloromethane was added and stirred at room temperature for 16hr. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5% HCl and brine solution. Concentration of the solvent followed by purification of the residue over column chromatography using 3% methanol-chloroform has provided N-(4-pyridyl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (120mg). Dry hydrochloric acid gas was bubbled through the ethereal solution of the amide for 10min so that solid material was separated out. Evaporation of the solvent and tituration of the residue with pentane gave solid hydrochloride salt of the above tilled amide; mp : 162-164°C ;

IR(KBr, ν_{max}) : 3298, 3074, 2976, 2870, 1688, 1633, 1601, 1558, 1504, 1469, 1318, 1279, 1183, 1121, 1035, 811,751, 519 cm^{-1} ;

EXAMPLE 40

Preparation of O-(3-Nitrophenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzo-dioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

To a solution of m-nitroaniline(276mg, 2 equiv.,) and diisopropyl-ethylamine (0.5mL) dissolved in 5 mL of dichloromethane cooled to -30°C, was added a solution of triphosgene (230mg,0.8mM) in 5 mL of dichloror-methane and the contents were stirred for 6h under N_2 atmosphere by allowing the temperature to come to r.t. Then this solution was transferred via cannula to another RB flask containing a solution of (3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl)phenylketoxime(315mg,1mM) and diisopropylethyl amine (0.2mL) dissolved in 5 mL of dichlorormethane at r.t. and stirred the reaction mixture for 16h. The reaction mixture was poured into ice water and extracted with chloroform. The organic extract was washed with water, 5% HCl, brine and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over silica gel column using chloroform produced a sticky solid(100mg) material of O-(3-nitrophenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime as a mixture of E & Z isomers.; mp : 56-58 °C ;

IR(KBr, ν_{max}) : 3350, 3084, 2874, 1742, 1531, 1506, 1432, 1349, 1328, 1274, 1200, 1027, 991, 737, 698 cm^{-1};

^1H NMR($CDCl_3$, 300MHz) : δ 8.60(br s, 1H), 8.32(s, 1H), 8.01(d, J=8Hz,1H), 7.98(d, J=8Hz,1H), 7.58-7.35(m,6H), 7.16(s, 1H), 7.18-

6.90(m,3H), 4.40-4.32(m,2H), 4.14(dd, J_1=12Hz, J_2=9Hz,1H), 3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.58(q, J=9Hz,2H), 1.21(t, J= 8Hz, 3H);

EXAMPLE 41

Preparation of O-(2,5-Dichlorophenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5;

Step 4

To a solution of 2,5-dichloroaniline(320mg, 2 equiv.,) and diisopropyl-ethylamine (0.5mL) dissolved in 5 mL of dichloromethane cooled to -30°C, was added a solution of triphosgene (236mg,0.8mM) in 5 mL of dichlorormethane and the contents were stirred for 6h under N2 atmosphere by allowing the temperature to come to r.t. Then this solution was transferred via cannula to another RB flask containing a solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (315mg,1mM) and diisopropylethyl amine (0.2mL) dissolved in 5 mL of dichlorormethane at r.t. and stirred the reaction mixture for 16h. The reaction mixture was poured into ice water and extracted with chloroform. The organic extract was

washed with water, 5% HCl, brine and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over silica gel column using 7% ethyl acetate-pet.ether produced a sticky solid(110mg) material of O-(2,5-dichloro phenyl aminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime as a mixture of E & Z isomers.; mp : 127 °C ;

IR(KBr, ν_{max}) : 3346, 3084, 2873, 1750, 1575, 1508, 1445, 1330, 1275, 1184, 1093, 1053, 983, 877, 698 cm^{-1};

^1H NMR($CDCl_3$, 300MHz) : δ 8.40(br s, 1H), 7.62-6.90(m,11H), 4.40-4.32(m,2H), 4.04(dd, J_1=12Hz, J_2=9Hz,1H), 3.69(qd, J_1=12 Hz, J_2=6Hz, 2H), 3.58(q, J=9Hz,2H), 1.24(t, J= 8Hz, 3H).

EXAMPLE 42

Preparation of O-(4-Trifluoromethylphenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime

Step 1

Initially 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step-1 of the Example-5.

Step 2

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone was prepared from 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl methanol as described in the step-2 of Example 5.

Step 3

3-Ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime was prepared from 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketone as described in step-3 of the Example-5.

Step 4

To a solution of 4-trifluoromethylaniline (600mg, 2 equiv.,) and diisopropyl-ethylamine (0.5mL) dissolved in 10mL of dichloromethane cooled to -30°C, was added a solution of triphosgene (440mg,1.49mM) in 5 mL of dichlorormethane and the contents were stirred for 6h under N_2 atmosphere by allowing the temperature to come to r.t. Then this solution was transferred via cannula to another RB flask containing a solution of 3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl phenyl ketoxime (500mg, 1.59mM) and diisopro-pylethylamine(0.2mL) dissolved in 5 mL of dichlorormethane at r.t. and stirred the reaction mixture for 16h. The reaction mixture was poured into ice water and extracted with chloroform. The organic extract was washed with water, 5% HCl, brine and dried over anh. sodium sulfate. Concentration of the solvent and purification of the residue over silica gel column using 2% acetone-chloroform produced a solid (200mg) material of O-(4-trifluoromethylphenylaminocarbonyl)-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]phenyl ketoxime as a mixture of E & Z isomers. mp : 60-62°C :

IR(KBr, ν_{max}) : 3276, 3084, 2877, 1739, 1615,1529, 1506, 1412, 1325, 1274, 1203,1184,1165,1115,1067, 987, 841, 697 cm^{-1} ;

EXAMPLE 43

Preparation of 1-[3-(N,N-Diethylaminomethyl)-2,3-dihydro benzodioxin-6-yl]-1-(3-chlorophenyl)-1-(2,5-dichorobenzyloxy) methane

Step 1

To freshly dried magnesium turnings (0.58g, 2 equiv.,) suspended in dry THF (10mL) was added a pinch of iodine followed by a solution of 3-chlorobromobenzene (4.6g, 2 equiv.,) in THF (10mL) and the contents were stirred at room temperature for 1h so that the magnesium is consumed to form grignard reagent. A solution of 3-(N,N-diethylaminomethyl)-6-formyl-

2,3-dihydrobenzodioxane (Intermediate 5) (3.0g, 0.012mol) in dry THF (10mL) was slowly added to the above reaction mixture over a period of 20min. and the contents were continued to stir for an additional 1h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether. The organic layer was thoroughly washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded crude 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) metha-nol (3.0g) as pale brown thick liquid which was used as such in the next step.

IR (neat, ν_{max}): 3349, 2972, 2935, 2874, 1593, 1505, 1473, 1435, 1274, 1077, 1034, 886, 771, 737 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 7.39 (s, 1H), 7.27-7.24 (m, 4H), 6.86 (d, J=9Hz, 1H), 6.83 (s, 1H), 4.35 (dd, J=16Hz, 2H), 4.23 (m, 1H), 3.99 (qd, J=16Hz, J=10Hz, 2H), 2.82-2.62 (m, 4H), 1.06 (t, 6H).

Step 2

To a pre-washed suspension of sodium hydride (80mg, 2 equiv., 60% oil dispersion) in N,N-dimethylformamide (5mL) was added a solution of 1-[3-(N,N-diethyl aminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol (300mg, 0.83mmol) in 2mL of N,N-dimethylformamide. Then a solution of 2,5-dichlorobenzylbromide (0.298g, 2.0 equiv.,) in N,N-dimethylformamide (5mL) was added to the above reaction mixture and the contents were heated to 60°C for 1h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 140mg of 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl)-1-(2,5-dichlorobenzyloxy) methane as a thick liquid after purification over silica gel column chromatography using 15% acetone-chloroform as eluent;

IR (neat, ν_{max}) 2969, 2929, 2871, 1592, 1505, 1467, 1435, 1275, 1205, 1097, 1042, 878, 813, 774 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz) : δ 7.38-7.13 (m, 7H), 6.88-6.84 (m, 3H), 5.40 (s, 1H), 4.74 (s, 2H), 4.35 (dd, J=16Hz, 2H), 4.23 (m, 1H), 3.99 (qd, J=16Hz, J=10Hz, 2H), 2.82-2.62 (m, 4H), 1.07 (t, 6H).

EXAMPLE 44

Preparation of 1-[3-(N,N-Diethylaminomethyl)-2,3-dihydro benzodioxin-6-yl]-1-(3-chlorophenyl)-1-(3-fluorobenzyloxy) methane

Step 1

Initially 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol was prepared from 3-(N,N-diethylamino-methyl)-6-formyl-2,3-dihydrobenzodioxane as described in step 1 of Example 43.

Step 2

To a pre-washed suspension of sodium hydride (80mg, 2 equiv., 60% oil dispersion) in THF (5mL) was added a solution of 1-[3-(N,N-diethyl-amino-methyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol (300mg, 0.83mmol) in THF (3mL) at 25°C. Then a solution of 3-fluorobenzylbromide (0.238g, 1.5 equiv.,) in THF (5mL) was added to the above reaction mixture and the contents were refluxed for 1h. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded an oily residue which was purified over silica gel column chromatography using 15% acetone-chloroform as eluent to furnish 110mg of 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzo-dioxin-6-yl]-1-(3-chlorophenyl)-1-(3-fluorobenzyloxy) methane as a thick pale brown liquid.

IR (neat, ν_{max}): 2969, 2930, 2871, 1592, 1505, 1435, 1275, 1075, 1034, 780 cm^{-1}.

EXAMPLE 45

Preparation of [3-(N,N-Diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone oxime ethyl ether

Step 1

Initially 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol was prepared from 3-(N,N-diethylaminomethyl)-6-formyl-2,3-dihydrobenzodioxane as described in step 1 of Example 43.

Step 2

To a suspended solution of pyridinium dichromate (PDC) (4.6g, 1.1 equiv.,) in dichloromethane (50mL) was added a solution of 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol (4.0g, 0.0111mol) dissolved in dichloromethane (30mL) at ice temperature. The reaction mixture was stirred for 2h by warming it to room temperature and quenched with 10mL of dry ether. The organic layer was decanted and filtered through a celite pad. The filtrate was concentrated to dryness to obtain [3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl mathanone (1.4g) as a pale yellow viscous liquid after purification over silica gel column chromatography using 15% acetone-chloroform as eluent;

IR (neat, ν_{max}) 2968, 2927, 2873, 1656, 1605, 1580, 1505, 1433, 1275, 1075, 744 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 7.7 (s, 1H), 7.61 (d, J=7.8Hz, 1H), 7.53 (d, J=8.4Hz, 1H), 7.41-7.31 (m, 3H), 6.95 (d, J=8.4Hz, 1H), 4.42 (m, 1H), 4.39 (dd, J=11.4Hz, 2H), 4.13 (qd, J=11.4Hz, J=6.6Hz, 2H), 2.83-2.78 (m, 4H), 1.14 (t, 6H).

Step 3

To a solution of [3-(N,N-diethylaminomethyl)-2,3-dihydrobenzo-dioxin-6-yl]-3-chlorophenyl methanone (1.4g, 0.0039mol) in methanol (30mL) was added hydroxylamine hydrochloride (0.677g, 2.5 equiv.,) and the contents were refluxed for 5h in presence of pyridine (5mL). The solvent was evaporated and the residue was poured into water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of solvent provided 1.25g of [3-(N,N-diethylaminomethyl)-2,3-dihydrobenzo-dioxin-6-yl]-3-chlorophenyl methanone oxime as a thick liquid;

IR (neat, ν_{max}): 2970, 2927, 2873, 1581, 1506, 1429, 1316, 1272, 1078, 966, 881, 749 cm^{-1}.

Step 4

To a pre-washed suspension of sodium hydride (75mg, 2 equiv., 60% oil dispersion) in THF (5mL) was added a solution of [3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone oxime (300mg, 0.80mmol) in THF (3mL). Then a solution of ethylbromide (0.13g, 1.5 equiv.,) in THF (3mL) was added to the above reaction mixture and the contents were refluxed for 1.5h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 90mg of E & Z isomeric mixture of [3-N,N-diethylaminomethyl-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone oxime ethyl ether as a thick liquid after purification over silica gel column chromatography using 20% acetone-chloroform as eluent;

IR (neat, ν_{max}): 2971, 2931, 2874, 1584, 1505, 1429, 1319, 1273, 1078, 1053, 816, 741, 697 cm^{-1};

^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.51 (s, 1H), 7.38-7.28 (m, 2H), 7.21 (d, 1H), 6.98-6.94 (d, 2H), 6.90 (m, 1H), 4.42-4.16 (m, 4H), 4.07-3.95 (m, 1H), 2.79-2.54 (m, 6H), 1.37 (t, 3H), 1.05 (t, 6H).

EXAMPLE 46

Preparation of O-(3-Chlorobenzyl)-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methnanone oxime

Step 1

Initially 1-[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol was prepared from 3-(N,N-diethylaminomethyl)-6-formyl-2,3-dihydrobenzodioxane as described in step 1 of Example 43.

Step 2

[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone was prepared from 1-[3-(N,N-diethylamino-methyl)-2,3-dihydrobenzodioxin-6-yl]-1-(3-chlorophenyl) methanol as described in step 2 of Example 45.

Step 3

[3-(N,N-diethylaminomethyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone oxime was prepared from 1-[3-(N,N-diethylaminomethyl)-2,3-dihydro benzodioxin-6-yl]-1-(3-chlorophenyl) methanone as described in step 3 of Example 5.

Step 4

To a pre-washed suspension of sodium hydride (38mg, 2 equiv., 60% oil dispersion) in THF (3mL) was added a solution of [3-(N,N-diethylamino-methyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlorophenyl methanone oxime (150mg, 0.40mmol) in THF (2mL). Then a solution of 3-chlorobenzyl-bromide (0.12g, 2.0 equiv.,) in THF (2mL) was added to the above reaction mixture and the contents were refluxed for 1h. Reaction was quenched with

water and extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification of the residue by column chromatography using 20% acetone-chloroform as a eluent furnished a 60:40 mixture of E & Z isomers of O-(3-chlorobenzyl)-[3-(N,N-diethylamino-methyl)-2,3-dihydrobenzodioxin-6-yl]-3-chlo-rophenyl methanone oxime as a thick liquid (90mg); IR (neat, ν_{max}): 2969, 2930, 2872, 1574, 1505, 1472, 1429, 1318, 1272, 1206, 1077, 876, 780 cm^{-1}.

EXAMPLE 47

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(2,5-dichlorobenzyloxy) methane

Step 1

To a solution of n-butyl lithium (34.2mL, 2 equiv., 15% solution in n-hexane) cooled to -78°C was added a solution of 2-bromopyridine (12.56g, 2 equiv.,) in THF (20mL). The contents were stirred for 10min. at –78°C and was added drop wise a solution of 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (9.0g, 0.04mol) (Intermediate 1) in THF (25mL) over a period of 10min. The reaction mixture was stirred at –78°C for 30min. and quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was thoroughly washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 5.5g of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol after silica gel column chromatography using 30% ethyl acetate-pet. ether as eluent.

IR (neat, νmax): 3378, 3060, 2975, 2928, 2874, 1592, 1505, 1435, 1275, 1208, 1145, 1117, 1039, 876, 806, 754 cm^{-1}.

Step 2

To a pre-washed suspension of sodium hydride (265mg, 2 equiv., 60% oil dispersion) in THF (10mL) was added a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (1.0g, 0.66mmol) in 15mL of THF. Then a solution of 2,5-dichlorobenzylbromide (1.58g, 2 equiv.,) in THF (5mL) was added to the above reaction mixture and the contents were stirred under reflux for 1h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification of the residue over silica gel column chromatography using 15% ethylacetate-pet.ether as eluent afforded of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(2,5-dichlorobenzyloxy) methane (800mg) as a viscous liquid which solidified slowly on standing; m.p : 85°C;

IR (KBr, ν_{max}): 3063, 2975, 2873, 1590, 1505, 1468, 1434, 1276, 1098, 1042, 877, 810, 752 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 8.52 (d, 1H), 7.72 (m, 1H), 7.59 (m, 2H), 7.21 (m, 3H), 6.97 (m, 2H), 6.84 (d, 1H), 5.51 (s, 1H), 4.6 (d, 2H), 4.28 (d, J=10Hz, 2H), 4.06 (m, 1H), 3.66 (m, 2H), 3.58 (q, 2H), 1.20 (t, 3H).

EXAMPLE 48

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(4-fluorobenzyloxy) methane

Step 1

Initially 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step 1 of Example 47.

Step 2

To a pre-washed suspension of sodium hydride (48mg, 1.5 equiv., 60% oil dispersion) in THF (3mL) was added a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (200mg, 0.66mmol) in 3mL of THF. Then a solution of 4-fluorobenzylbromide (0.149g, 1.2 equiv.,) in THF (4mL) was added to the above reaction mixture and the contents were refluxed for 1h. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 90mg of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(4-fluorobenzyloxy) methane as a thick liquid after purification over silica gel column chromatography using 15% ethylacetate-pet. ether as eluent;

IR (neat, ν_{max}: 3052, 2925, 2871, 1590, 1508, 1435, 1275, 1223, 1116, 1039, 824, 753 cm^{-1}.

EXAMPLE 49

Preparation of 1-(3-Butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(2,5-dichlorobenzyloxy) methane

Step 1

To a solution of n-butyl lithium (34.2mL, 2 equiv., 15% solution in n-hexane) cooled to -78°C was added a solution of 2-bromopyridine (12.56g, 2 equiv.,) in THF (20mL). The contents were stirred for 10min. at –78°C and to this was added drop wise a solution of 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane (10.0gm, 0.040mol) (Intermediate 2) in THF (25mL) over a period of 10min. The reaction mixture was stirred at –78°C for 30min. and quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was thoroughly washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent

afforded 5.6g of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol after silica gel column chromatography using 30% ethylacetate-pet.ether as eluent;

IR(neat, ν_{max}): 3394, 2957, 2932, 2871, 1592, 1505, 1435, 1275, 1117, 1038, 878, 807, 753 cm^{-1}.

Step 2

To a pre-washed suspension of sodium hydride (87mg, 2 equiv., 60% oil dispersion) in THF (5mL) was added a solution of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (300mg, 0.91mmol). Then a solution of 2,5-dichlorobenzylbromide (0.437g, 1.5 equiv.,) in THF (5mL) was added to the above reaction mixture and the contents were refluxed for 1h. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 150mg of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(2,5-dichlorobenzyloxy) methane as a thick liquid after column chromatography using 15% ethyl acetate-pet.ether as eluent;

IR (neat, ν_{max}): 2933, 2957, 2871, 1590, 1505, 1467, 1434, 1275, 1097, 1042, 878, 810, 751 cm^{-1}, 1H NMR ($CDCl_3$, 300MHz) δ 8.52 (d, J=4.5Hz, 1H), 7.72 (m, 1H), 7.59 (m, 2H), 7.23 (m, 4H), 6.97 (m, 2H), 6.84 (d, J=8.4Hz, 1H), 5.51 (s, 1H), 4.6 (qd, J=18.6Hz, J=13.5Hz, 2H), 4.28 (d, J=9.5Hz, 2H), 4.06 (m, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 1.57 (m, 2H), 1.37 (m, 2H), 0.90 (t, 3H).

EXAMPLE 50

Preparation of 1-(3-Butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(3-fluorobenzyloxy) methane

Step 1

Initially 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 2) as described in step 1 of Example 49.

Step 2

To a pre-washed suspension of sodium hydride (87mg, 2 equiv., 60% oil dispersion) in THF (7.5mL) was added a solution of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (300mg, 0.911mmol). Then a solution of 3-fluorobenzylbromide (0.344g, 1.5 equiv.,) in THF (7.5mL) was added to the above reaction mixture and the contents were refluxed for 1h. The reaction mixture was quenched with water and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of the solvent afforded 150mg of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-1-(3-fluoro-benzyloxy) methane as a thick liquid after column chromatography using 15% ethyl acetate-pet.ether as eluent;

IR (neat, ν_{max}): 2957, 2933, 2871, 1590, 1505, 1434, 1275, 1098, 1038, 880, 751 cm^{-1}. ^1H NMR ($CDCl_3$, 300MHz): δ 8.52 (d, J=4.5Hz, 1H), 7.70 (t, J=7.8Hz, 1H), 7.57 (d, J=7.8Hz, 1H), 7.27 (m, 2H), 7.13 (m, 3H), 6.95 (m, 3H), 6.82 (d, J=8.4Hz, 1H), 5.45 (s, 1H), 4.60 (qd, J=18.6Hz, J=13.5Hz, 2H), 4.28 (d, J=9.5Hz, 2H), 4.06 (m, 1H), 3.66 (m, 2H), 3.46 (t, 2H), 1.57 (m, 2H), 1.39 (m, 2H), 0.90 (t, 3H).

EXAMPLE 51

Preparation of O-(4-Fluorobenzyl)-1-[3-(ethoxymethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone oxime

Step 1

Initially 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 2) as described in step 1 of Example 48.

Step 2

To a suspended solution of pyridinium dichromate (PDC) (2.29g, 1.0 equiv.,) in dichloromethane (25mL) was added a solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (2.0g, 0.0332mol) in dichloromethane (10mL) at ice temperature. The reaction mixture was then stirred at room temperature for 30min. and quenched with ether. The organic layer was decanted and filtered through a small pad of celite. The filtrate was concentrated to dryness to obtain 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone (1.2g) as a pale yellow viscous liquid after column chromatography;

IR (neat, ν_{max}): 3055, 2976, 2929, 2876, 1658, 1604, 1580, 1504, 1435, 1308, 1274, 1145, 1118, 1093, 1032, 995, 907, 830, 804, 748, 698 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz) : δ 8.73 (d, 1H), 8.01-7.85 (m, 2H), 7.73-7.65 (m, 2H), 7.51-7.44 (m, 1H), 6.99 (d, J=12.6Hz, 1H), 4.43-4.32 (m, 2H), 4.21-4.12 (m, 1H), 3.73-3.66 (m, 2H), 3.64 (q, 2H), 1.24 (t, 3H).

Step 3

To a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone (2.0g, 0.007mol) in methanol (25mL) was added hydroxylamine hydrochloride (1.16g, 2.5 equiv.,) and the contents were refluxed for 4h in the presence of pyridine (1mL). The solvent was

evaporated and the residue was poured into water. The aqueous layer was extracted with ethyl acetate and the organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Concentration of solvent provided 1.8g of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) metha-none oxime as a thick liquid;

IR (neat, ν_{max}): 3270, 2975, 2873, 1583, 1507, 1431, 1328, 1273, 1117, 1095, 1037, 959, 815, 749 cm^{-1}.

^1H NMR ($CDCl_3$, 300MHz) : δ 8.64 (d, J=4.5Hz, 1H), 7.82 (t, J=7.5Hz, 1H), 7.40-7.32 (m, 2H), 7.04-6.93 (m, 2H), 6.89 (d, J=8.4Hz, 1H), 4.35-4.26 (m, 2H), 4.13-4.07 (m, 1H), 3.73-3.53 (brm, 4H), 1.23 (t, 3H).

Step 4

To a pre-washed suspension of sodium hydride (50mg, 2 equiv., 60% oil dispersion) in N,N-dimethylformamide (4mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzo dioxin-6-yl]-1-(pyrid-2-yl)methanone oxime (200mg, 0.95mmol) in N,N-dimethylformamide (5mL). Then a solution of 4-fluorobenzylbromide (242mg, 2.0 equiv.,) in N,N-dimethylformamide (3mL) was added to the above reaction mixture and the contents were heated at 60°C for 1h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 240mg of O-(4-fluorobenzyl)-1-[3-(ethoxymethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone oxime as a mixture of E & Z isomers (60:40) after purification over silica gel column chromatography;

IR (neat, ν_{max}): 2922, 2873, 1584, 1506, 1474, 1274, 1118, 1098, 997, 820 cm-1;

^{1}H NMR ($CDCl_3$, 300MHz) : δ 8.64 (d, 2H), 7.69 (m, 2H), 7.41-7.24 (brm, 3H), 7.09-6.92 (brm, 5H), 5.26 (s, 2H), 4.38-4.29 (m, 2H), 4.16-4.10 (m, 1H), 3.71-3.53 (brm, 4H), 1.23 (t, 3H).

EXAMPLE 52

Preparation of O-(2,5-Dichlorobenzyl)-1-[3-(ethoxymethyl)-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone oxime

Step 1

Initially 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 2) as described in step 1 of Example 48.

Step 2

1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanone was prepared from 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol as described in step 2 of Example 51.

Step 3

1-[3-Ethoxymethyl-2,3-dihydrobenzo dioxin-6-yl]-1-(pyrid-2-yl) methanone oxime was prepared from 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanone as described in step 3 of Example 51.

Step 4

To a pre-washed suspension of sodium hydride (50mg, 2 equiv., 60% oil dispersion) in THF (5mL) was added a solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone oxime (200mg, 0.63mmol) in THF (5mL). Then a solution of 2,5-dichlorobenzylbromide (307mg, 2 equiv.,) in THF (5mL) was added to the above reaction mixture and the contents were refluxed for 1h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of

the solvent afforded 260mg crude O-(2,5-dichlorobenzyl)-1-[3-(ethoxy-methyl)-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone oxime as mixture of E & Z isomers which were separated by column chromatography using 15% ethyl acetate-pet.ether as eluent to give 70 mg of less polar and 90mg of the more polar isomers as thick liquid. More polar isomer :

IR (neat, ν_{max}):) 3059, 2975, 2927, 2873, 1584, 1505, 1465, 1427, 1330, 1274, 1119,1096, 1016, 949, 887,814, 793, 743, 688 cm^{-1}.

^1H NMR ($CDCl_3$, 300MHz): δ 8.73 (d, J=4.5Hz, 1H), 7.79 (t, J=6.0Hz, 1H), 7.47 (d, J=8.4Hz, 1H), 7.32-7.12 (brm, 4H), 6.99 (m, 2H), 6.81 (d, J=9.0Hz, 1H), 5.23 (s, 1H), 4.29 (m, 2H), 4.08 (m, 1H), 3.69-3.49 (m, 4H), 1.19 (t, 3H).

Less polar isomer :

EXAMPLE 53

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-fluorophenyl) ethylene

Step 1

Initially 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 1) as described in step 1 of Example 48.

Step 2

1-[3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl)methanone was prepared from 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol as described in step 2 of Example 51.

Step 3

To freshly dried magnesium turnings (96mg, 4 equiv.,) suspended in dry ether (10mL) was added a pinch of iodine followed by a solution of 3-fluorobenzylbromide (762mg, 4 equiv.,) in dry ether (10mL) over a period of

10min. The contents were stirred for 30min. at room temperature so that the magnesium is completely consumed to form Grignard reagent. A solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl)methanone (300mg, 1.0mmol) in dry ether (10mL) was added to the above solution over a period of 10min. and the reaction mixture was allowed to stir for additional 1h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-ethoxymethyl-2,3-dihydrobenzo-dioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-fluorophenyl)ethane (140mg) as a thick liquid after silica gel column chromatography using 20% ethyl acetate-pet.ether as eluent;

IR (neat, ν_{max}): 3363, 2976, 2928, 2874, 1589, 155, 1433, 1275, 1118, 1085, 873, 784, 749, cm^{-1}.

Step 4

A solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-fluorophenyl)ethane (140mg, 0.342mmol) in benzene (10mL) was treated with p-toluenesuphonic acid (259mg, 4 equiv.,) and the contents were heated to reflux for 5h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-fluorophe-nyl) ethylene (160mg) as a mixture of E & Z isomers which were separated by silica gel column chromatography using 18% ethyl acetate-pet.ether to give 20mg of the less polar and 70mg of the more polar isomers as thick liquids. More polar isomer :

IR (neat, ν_{max}): 2975, 2928, 2873, 1582, 1506, 1426, 1305, 1278, 1119, 1095, 1038, 874, 783, 751, 686 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 8.73 (d, 1H), 7.67-7.60 (m, 2H), 7.28-6.72 (m, 8H), 6.58 (d, 1H) 4.34-4.30 (d, 2H), 4.14-4.04 (m, 1H), 3.69-3.52 (m, 4H), 1.23 (t, 3H).

EXAMPLE 54

Preparation of 1-(3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-chlorophenyl) ethylene

Step 1

Initially 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 1) as described in step 1 of Example 48.

Step 2

1-[3-Ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl)methanone was prepared from 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol as described in step 2 of Example 51.

Step 3

To freshly dried magnesium turnings (96mg, 4 equiv.,) suspended in dry ether (10mL) was added a pinch of iodine followed by a solution of 3-chlorobenzylbromide (0.83g, 4 equiv.,) in dry ether (10mL) over a period of 10min. The contents were stirred for 30min. at room temperature so that the magnesium is completely consumed to form Grignard reagent. A solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone (300mg, 1.0mmol) in dry ether (10mL) was slowly added to the above solution over a period of 10min. and the reaction mixture was allowed to stir for additional 1h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate.

The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-chlorophenyl) ethane (180mg) as a thick liquid after passing through silica gel column chromatography using 20% ethyl acetate-pet.ether for purification;

IR (neat, ν_{max}): 3485, 2975, 2928, 2874, 1595, 1504, 1446, 1275, 1118, 1095, 878, 764, 701 cm^{-1}.

Step 4

A solution of 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-chlorophenyl)ethane (170mg, 0.342mmol) in benzene (10mL) was treated with p-toluenesuphonic acid (261mg, 4 equiv.,) and the contents were heated to reflux for 3h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-chloro phenyl) ethylene (120mg) as a mixture of E & Z isomers after column chromatography over silica gel using 20% ethyl acetate-pet.ether as thick liquid;

IR (neat,νmax): (more polar) 2975, 2927, 2872, 1582, 1505, 1425, 1305, 1278, 1119, 1095, 1038, 874, 750, 686 cm^{-1};

^{1}H NMR ($CDCl_3$, 300MHz): δ 8.67 (d, J=4.5Hz,1H), 7.61 (t, J= 7.5Hz, 1H), 7.21 (m, 1H), 7.14 (d, J=7.5Hz, 1H), 7.06-6.96 (m, 3H), 6.93 (s, 1H), 6.86 (s, 1H), 6.80 (m, 2H), 6.78 (d, J=6.9Hz, 1H), 4.30 (m, 2H), 4.09 (m, 1H), 3.69-3.49 (m, 4H), 1.20 (t, 3H).

EXAMPLE 55

Preparation of 1-(3-Butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-fluorophenyl) ethylene

Step 1

Initially 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 2) as described in step 1 of Example 49.

Step 2

To a suspended solution of pyridinium dichromate (PDC) (5.65g, 1.1 equiv.,) in dichloromethane (50mL) was added a solution of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol (4.5g, 0.014mol) in dichloromethane (10mL) at ice temperature. The reaction mixture was then stirred at room temperature for 30min. and quenched with ether. The organic layer was decanted and filtered through a small pad of celite. The filtrate was concentrated to dryness to obtain 1-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone (2.6g) as a pale yellow viscous liquid;

IR (neat, ν_{max}): 3056, 2957, 2932, 2871, 1657, 1604, 1580, 1504, 1435, 1308, 1274, 1208, 1116, 1093, 1032, 995, 896, 748, 698 cm^{-1}.

Step 3

To freshly dried magnesium turnings (58mg, 4 equiv.,) suspended in dry ether (10mL) was added a pinch of iodine followed by a solution of 3-fluorobenzylbromide (456mg, 4 equiv.,) in dry ether (10mL) over a period of 10min. The contents were stirred for 30min. at room temperature so that the magnesium is completely consumed to form Grignard reagent. A solution of 1-[3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl)methanone (200mg, 0.611mmol) in dry ether (10mL) was added to the above solution over a period of 10min. and the reaction mixture was allowed to stir for

additional 1h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-fluorophenyl) ethane (180mg) as a thick liquid after silica gel column chromatography using 20% ethyl acetate-pet.ether as eluent;

IR (neat, ν_{max}): 3350, 2958, 2932, 2871, 1589, 1505, 1487, 1275, 1118, 1086, 876, 786, 749,696 cm^{-1}.

Step 4

A solution of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-fluorophenyl)ethane (150mg, 0.342mmol) in benzene (10mL) was treated with p-toluenesuphonic acid (261mg, 4 equiv.,) and the contents were heated to reflux for 5h. The reaction was quenched with saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate, water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-fluoro phenyl) ethylene (110mg) as a mixture of E & Z isomers after silica gel column chromatography using 20% ethyl acetate-pet.ether as thick liquid;

IR (neat, ν_{max}: 2958, 2933, 2871, 1582, 1506, 1426, 1277, 1121, 1035, 874, 783, 750,686 cm^{-1};

^{1}H NMR ($CDCl_3$, 300MHz): δ 8.73 (d, 1H), 7.64-7.59 (m, 2H), 7.29-6.72 (m, 8H), 6.58 (d, 1H) 4.37-4.27 (d, 2H), 4.13-4.04 (m, 1H), 3.73-3.59 (m, 2H), 3.56-3.47 (t, 2H), 1.62-1.51 (m, 2H), 1.43-1.27 (m, 2H), 0.93 (t, 3H).

EXAMPLE 56

Preparation of 1-(3-Butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-chlorophenyl) ethylene

Step 1

Initially 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol was prepared from 3-butoxymethyl-6-formyl-2,3-dihydrobenzodioxane (Intermediate 2) as described in step 1 of Example 49.

Step 2

1-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl)methanone was prepared from 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl) methanol as described in step 2 of Example 55.

Step 3

To freshly dried magnesium turnings (58mg, 4 equiv.,) suspended in dry ether (10mL) was added a pinch of iodine followed by a solution of 3-chlorobenzylbromide (0.49g, 4 equiv.,) in dry ether (10mL) over a period of 10min. The contents were stirred for 30min. at room temperature so that the magnesium is completely consumed to form Grignard reagent. A solution of 1-[3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl]-1-(pyrid-2-yl) methanone (200mg, 0.611mmol) in dry ether (10mL) was slowly added to the above solution over a period of 10min. and the reaction mixture was allowed to stir for additional 1h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-chlorophenyl) ethane (180mg) as a thick liquid after passing through silica gel column chromatography using 20% ethylacetate-pet.ether for purification;

IR (neat, ν_{max}): 3349, 2957, 2931, 2870, 1591, 1503, 1431, 1275, 1117, 1082, 879, 751, 685 cm^{-1};

Step 4

A solution of 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-hydroxy-1-(pyrid-2-yl)-2-(3-chlorophenyl)ethane (150mg, 0.33mmol) in benzene (10mL) was treated with p-toluenesulphonic acid (25 1mg, 4 equiv.,) and the contents were heated to reflux for 4h. The reaction was quenched with saturated sodium bicarbonate solution and diluted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate, and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent afforded 1-(3-butoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-(pyrid-2-yl)-2-(3-chlorophenyl)ethylene (110 mg) as a mixture of E & Z isomers by silica gel column chromatography using 18% ethyl acetate-pet.ether as thick liquid;

IR (neat, ν_{max}): 2957, 2929, 2870, 1582, 1505, 1425, 1277, 1119, 1094, 1038, 811, 749, 685 cm^{-1} .

^1H NMR ($CDCl_3$, 300MHz): δ 8.67 (d, J=4.5Hz,1H), 7.61 (t, J= 7.5Hz, 1H), 7.23 (m, 1H), 7.14 (d, J=7.5Hz, 1H), 7.06-6.96 (m, 3H), 6.93 (s, 1H), 6.86 (s, 1H), 6.80 (m, 2H), 6.78 (d, J=6.9Hz, 1H), 4.31 (m, 2H), 4.09 (m, 1H), 3.69-3.54 (m, 4H), 3.50 (t, 2H), 1.58 (m, 2H), 1.39 (m, 2H), 1.20 (t, 3H).

EXAMPLE 57

Preparation of N-(4-Trifluoromethylphenyl)-3-cyclopropylmethoxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

To a solution of 3-cyclopropylmethoxymethyl-6-formyl-2,3-dihydrobenzo dioxane (2.0g, 8.1mmol) (Intermediate 6) in acetone-water mixture in 2: 1 ratio (20mL) was added sulfamic acid (1.173g, 1.5 equiv.)

while stirring at 0°C. A solution of 80% sodium chlorite (0.911g, 1.2 equiv.,) in water (2.0mL) was added drop wise to the above reaction mixture over a period of 10min. and was allowed to stir at 0°C for additional 30min. The reaction mixture was then diluted with water (20mL) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of organic solvent afforded of 3-cyclopropyl methoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid as a white solid (1.7g);

mp : 115°C ;

^{1}H NMR ($CDCl_3$, 300MHz): δ 7.68 (s, 1H), 7.67 (d, J=8.4Hz, 1H), 6.95 (d, J=8.4Hz, 1H), 4.42-4.35 (m, 2H), 4.19-4.12 (m, 1H), 3.82-3.70 (dd, J=11Hz, J=4.5Hz, 1H), 3.69-3.63 (dd, J=11Hz, J=6.0Hz, 1H), 3.38 (d, J=6.9Hz, 2H), 1.08 (m, 1H), 0.56 (m, 2H), 0.23 (m, 2H).

Step 2

A solution of 3-cyclopropylmethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid (250mg, 0.946mmol) in freshly distilled thionyl chloride (5mL) was heated to reflux temperature for 1.5h. The excess thionyl chloride was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 3

To a solution of 4-trifluoromethylphenyl aniline (167mg, 1.0 equiv.) and N,N-diisopropylethyl amine (0.5mL) in THF (10mL), a solution of above acid chloride (from step 2) in THF (5mL) was added at 0°C and the solution was allowed to warm to room temperature and further stirred at room temperature for 3-4h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5% HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 10% ethylacetate-

pet.ether provided N-(4-trifluoromethylphenyl)-3-cyclopropylmethoxy-methyl-2,3-dihydrobenzodioxinyl-6-carboxamide (180mg) as a white solid;

mp:152°C;

IR (KBr,νmax): 3335, 2974, 2873, 1651, 1615, 1526, 1506, 1406, 1331, 1286, 1164, 1129, 1113, 1068, 833, 757, 670 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 7.82 (s, 1H), 7.74 (d, J=8.4Hz, 1H), 7.60 (d, J=8.4Hz, 1H), 7.42 (s, 1H), 7.37 (d, J=8.4Hz, 1H), 6.95 (d, J=8.4Hz, 1H), 4.40 (m, 2H), 4.17 (m, 1H), 3.78 (dd, J=9.0Hz, J=4.5Hz, 1H), 3.69 (dd, J=10.5Hz, J=6.0Hz, 1H), 3.38 (d, J=7.0Hz, 2H), 1.54 (s, 3F), 1.09 (m, 1H), 0.59 (m, 2H), 0.28 (m, 2H).

EXAMPLE 58

Preparation of N-(3,5-Dichloropyrid-4-yl)-3-cyclopropylmethoxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

Initially 3-cyclopropylmethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid was prepared from 3-cyclopropylmethoxymethyl-6-formyl-2,3-dihydrobenzo dioxane as described in steps 1 of Example 57.

Step 2

Initially 3-cyclopropylmethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid chloride was prepared from 3-cyclopropylmethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid as described in steps 2 of Example 57.

Step 3

To a pre-washed suspension of sodium hydride (111mg, 1.0 equiv., 60% oil dispersion) in THF (5mL) was added drop wise a solution of 4-amino-3,5-dichloropyridine (189mg, 1.0 equiv.) in THF (5mL) at –10°C. A pre-cooled solution of above acid chloride (from step 1) in THF (5mL) was added, all at once, to the reaction mixture and the contents were stirred at –

10°C for 30min. The reaction was quenched with brine, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, 5 %HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 30%ethylacetate-pet.ether provided N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxymethyl -2,3-dihydro benzodioxinyl-6-carboxamide as a white solid (90mg);

mp:114°C ;

IR (KBr, ν_{max}): 3257, 2973, 2923, 2874, 1661, 1585, 1486, 1282, 1096, 1029, 885, 818, 754 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 8.52 (s, 2H), 7.60 (s, 1H), 7.49 (s, 1H), 7.47 (d, J=8.4Hz, 1H), 6.98 (d, J=8.4Hz, 1H), 4.42-4.35 (m, 2H), 4.19-4.12 (m, 1H), 3.79-3.74 (dd, J=11Hz, J=4.5Hz, 1H), 3.70-3.64 (dd, J=11Hz, J=6.0Hz, 1H), 3.37 (d, J=6.9Hz, 2H), 0.85 (m, 1H), 0.56 (m, 2H), 0.21 (m, 2H).

EXAMPLE 59

Preparation of N-(4-Trifluoromethyphenyl)-3-methansulfonyloxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

Initially 3-methanesulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3-hydroxymethyl-6-formyl-2,3-dihydroxybenzodioxane as described in step 2 of Intermediate 4.

Step 2

To a solution of 3-methansufonyloxymethyl-6-formyl-2,3-dihydrobenzo dioxane (8.0g, 0.029mol) (Intermediate 4) in acetone-water mixture in 2: 1 ratio (90mL) was added sulfamic acid (4.2g, 1.5 equiv.) while stirring at 0°C. A solution of 80% sodium chlorite (3.60g, 1.2 equiv.,) in water (2.0mL) was added drop wise to the above reaction mixture over a period of 10min. and was allowed to stir at 0°C for additional 30min. The

reaction mixture was then diluted with water (20mL) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of organic solvent afforded of 3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid as a white solid (7.4g); mp :128°C

Step 3

A solution of 3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid (150mg, 0.52mmol) and freshly distilled thionyl chloride (2mL) in dry benzene (2mL) was heated to reflux temperature for 2h. The excess thionyl chloride/benzene was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 3

To a solution of 4-trifluoromethylaniline (92mg, 1.1 equiv.) and N,N-diisopropylethylamine (0.25mL) in THF (1mL), a solution of above acid chloride (from step 2) in THF (1mL) was added at 0°C and the solution was allowed to warm to room temperature and further stirred at room temperature for 1h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5% HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 15% acetone-chloroform provided N-(4-trifluoromethylphenyl)-3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (100mg) as a white solid;

mp: 164°C ;

IR (KBr, νmax): 3339, 3041, 2944, 1650, 1612, 1534, 1505, 1407, 1335, 1286, 1173, 1115, 970, 832, 755, 528 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 9.57 (s, 1H), 7.90 (d, J=8.4Hz, 1H), 7.63-7.34 (m, 4H), 6.95 (d, J=8.4Hz, 1H), 4.54-4.39 (m, 4H), 4.20-4.14 (qd, J=11.7Hz, J=6.6Hz, 1H), 3.12 (s, 3H).

EXAMPLE 60

Preparation of N-Cyclopentyl-3-methansulfonyloxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

Initially 3-methanesulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3-hydroxymethyl-6-formyl-2,3-dihydroxybenzodioxane as described in step 2 of Intermediate 4.

Step 2

Initially 3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid was prepared from 3-methanesulfonyloxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step 2 of Example 59.

Step 3

A solution of 3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid (150mg, 0.52mmol) and freshly distilled thionyl chloride (2mL) in dry benzene (2mL) was heated to reflux temperature for 2h. The excess thionyl chloride/benzene was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 4

To a solution of cyclopentylamine (49mg, 1.1 equiv.) and N,N-diisopropylethyl amine (0.25mL) in THF (1mL), a solution of above acid chloride (from step 2) in THF (1mL) was added at 0°C and the solution was allowed to warm to room temperature and further stirred at room temperature for 1h. The reaction was quenched with water and extracted with chloroform. The organic layer was washed with water, 5% HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 15% acetone-chloroform provided N-(cyclopentyl)-3-methanesulfonyloxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide (85mg) as a white solid;

mp: 120°C ; mp: 120°C ;

IR (KBr, vmax): 3312, 2959, 2871, 1634, 1584, 1539, 1498, 1355, 1277, 1175, 1036, 969, 826, 736, 527 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 7.32-7.24 (m, 2H), 6.90 (d, J=4.5Hz, 1H), 5.90 (brs, 1H), 4.43-4.32 (m, 4H), 4.16 (m, 1H), 3.08 (s, 3H), 2.08 (m, 2H), 1.69-164 (m, 5H), 1.49 (m, 2H).

EXAMPLE 61

Preparation of N-(3,5-dichloropyrid-4-yl)-3-(tert.butyldimethylsilyloxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

Initially 3-tert.butyldimethylsilyloxymethyl-6-formyl-2,3-dihydrobenzodioxane was prepared from 3-hydroxymethyl-6-formyl-2,3-dihydroxybenzodioxane as described in step 2 of Intermediate 7.

Step 2

To a solution of 3-tert.butyldimethylsilyloxymethyl-6-formyl-2,3-dihydrobenzodioxane (1.4g, 4.5mmol) (Intermediate 7) in acetone-water mixture in 2: 1 ratio (20mL) was added sulfamic acid (0.66g, 1.5 equiv.) while stirring at 0°C. A solution of 80% sodium chlorite (0.492g, 1.2 equiv.,) in water (2.0mL) was added drop wise to the above reaction mixture over a period of 10min. and was allowed to stir at 0°C for additional 30min. The reaction mixture was then diluted with water (20mL) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of organic solvent afforded of 3-tert.butyldimethylsilyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid as pale yellow solidl (1.4g).

mp.; 90-92 °C ;

^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.60 (m, 2H), 6.86 (d, J=8.4Hz, 1H), 4.38 (d, J=11Hz, 1H), 4.20 (m, 2H), 3.95 (dd, J=11Hz, J=4.5Hz, 1H), 3.82 (dd, J=11Hz, J=6.0Hz, 1H), 0.89 (s, 9H), 0.10 (s, 6H).

Step 3

A solution of 3-tert.butyldimethylsilyloxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid (1.4g, 4.43mmol) and freshly distilled thionyl chloride (5mL) in dry benzene (5mL) was heated to reflux temperature for 2h. The excess thionyl chloride/benzene was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 4

To a pre-washed suspension of sodium hydride (440mg, 2.0 equiv., 60% oil dispersion) in N,N-dimethylformamide (5mL) was added drop wise a solution of 4-amino-3,5-dichloropyridine (704mg, 1.0 equiv.) in N,N-dimethylformamide (10mL) at -10°C. A pre-cooled solution of above acid chloride (from step 1) in THF (10mL) was added, all at once, to the reaction mixture and the contents were stirred at –10°C for 30min. The reaction was quenched with brine, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, 5% HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 30%ethylacetate-pet.ether provided N-(3,5-dichloropyrid-4-yl)-3-tert.butyldimethylsilyloxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide as a white solid (90mg);

mp: 58°C ;

IR (KBr, ν_{max}): 3257, 2953, 2927, 2856, 1662, 1612, 1586, 1551, 1486, 1400, 1283, 1100, 1033, 883, 837, 779, 755 cm^{-1};

^{1}H NMR ($CDCl_3$, 300MHz):- δ 8.54 (s, 2H), 7.58 (s, 1H), 7.48 (d, J=2Hz, 1H), 7.44 (dd, J=8.4Hz, J=2Hz, 1H), 6.96 (d, J=8.4Hz, 1H), 4.38 (dd,

J=11Hz, J=1.8Hz, 1H), 4.22 (m, 1H), 4.14 (dd, J=11Hz, J=8Hz, 1H), 3.93 (dd, J=11Hz, J=4.5Hz, 1H), 3.78 (dd, J=11Hz, J=6.0Hz, 1H), 0.84 (s, 9H), 0.11 (s, 6H).

EXAMPLE 62

Preparation of N-(3,5-Dichloropyrid-4-yl)-3-(ethoxymethyl -2,3-dihydrobenzodioxinyl-6-carboxamide

Step 1

Initially 3-ethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid was prepared from 3-ethoxymethyl-6-formyl-2,3-dihydrobenzodioxane as described in step 1 of Example 30.

Step 2

A solution of 3-ethoxymethyl-2,3-dihydrobenzodioxane-6-carboxylic acid (300mg, 1.26mmol) and freshly distilled thionyl chloride (2mL) in dry benzene (2mL) was heated to reflux temperature for 1.5h. The excess thionyl chloride/benzene was removed under vacuum to get the corresponding acid chloride which was subjected the next reaction as such.

Step 3

To a pre-washed suspension of sodium hydride (120mg, 2.0 equiv., 60% oil dispersion) in N,N-dimethylformamide (5mL) was added drop wise a solution of 4-amino-3,5-dichloropyridine (205mg, 1.0 equiv.) in N,N-dimethylformamide (10mL) at -10°C. A pre-cooled solution of above acid chloride (from step 2) in THF (6mL) was added, all at once, to the reaction mixture and the contents were stirred at –10°C for 30min. The reaction was quenched with brine, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, 5% HCl and brine solution. Evaporation of solvent followed by purification of the residue over silica gel column chromatography using 30%ethylacetate-pet.ether provided N-(3,5-

dichloropyrid-4-yl)-3-ethoxymethyl-2,3-dihydrobenzodioxinyl-6-carboxamide as a white solid (150mg);

mp: 110°C ;

IR (KBr, ν_{max}): 3259, 3062, 2954, 2925, 2872, 1661, 1611, 1585, 1550, 1486, 1400, 1282, 1195, 1118, 1032, 886, 818, 754 cm^{-1};

^1H NMR ($CDCl_3$, 300MHz): δ 8.54 (s, 2H), 7.66 (s, 1H), 7.53 (d, J=2Hz, 1H), 7.49 (dd, J=8.4Hz, J=2Hz, 1H), 7.02 (d, J=8.4Hz, 1H), 4.42-4.32 (m, 2H), 4.19-4.09 (m, 1H), 3.76-3.65 (m, 2H), 3.64-3.55 (q, 2H), 1.23 (t, 3H).

The compounds of the general formula **1** described in the present invention are novel and constitute a different heterocyclic moiety as their part structure. Therefore these structural class of compounds may impart a distinctly different steric environment around the molecule so that it may lead to a potent PDE4 inhibitory activity and selective PDE4 isozyme inhibition. Indeed, as shown below, some of the compounds of the formula **1** have shown very potent human PDE4 inhibition activity in an *in vitro* assay system, compared to Rolipram or Ariflo, a compound presently in advanced stage of Phase-III clinical trials. Hence the present invention provides a novel series of heterocyclic compounds having potential therapeutic activity and medical use against several allergic disorders, particularly in asthma.

Assay methods

I) In vitro

Phosphodiesterase (PDE4) enzyme partially purified from human U-937 pronocytic cells is used. Test compound / vehicle is incubated with 0.2 g enzyme and 1M cAMP containing 0.01M [^3H] cAMP in Tris buffer pH 7.5 for 20minutes at 30°C. The reaction is terminated by boiling for 2 minutes and resulting AMP is converted to adenosine by addition of 10 mg/ml snake venom nucleotidase and further incubation at 30°C for 10

minutes. Unhydrolyzed cAMP is bound toAGI-X2 resin, and remaining [^{3}H] adenosine in the aqueous phase is quantitated by scintillation counting. Compounds are generally screened at various concentrations to determine their IC_{50} values.

In order to determine the specificity of the compounds against various PDE isoenzymes the following sources were used in the present assay:

PDE1: Purified from Guinea Pig Trachea by anion exchange followed by hydrophobic interaction chromatography. Guinea Pig Trachea isolated PDE1 is identical in kinetic behavior to the human gene product.

PDE2: Human gene clone product obtained from Pfizer Laboratories, France.

PDE3: Purified from dog aorta by affinity chromatography using modified immobilized AMP. Sensitive toCilostimide.

PDE4: We have initially used U 937 cells as source of PDE4 enzymes as it has most of the complex isozymes in this class. As some amount of PDE3 (< 9 %) contaminates PDE4, we specifically used Siguazodan / Cilostimide in a Mono Q chromatography procedure to identifyPDE4 versus PDE3 pools.

PDE5: Purified and separated from PDE1 Guinea Pig trachea. Sensitive to Sildenafil citrate.

PDE6: Purified and separated from human retinal rods.

(II) ***In vivo***

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula **1** are standard assay procedures as disclosed by Schilling et al, Anal. Biochem. 216: 154 (1994), Thompson and Strada, Adv.Cycl. Nucl. Res. 8: 119 (1979) and Gristwood and Owen, Br. J.Pharmacol. 87: 91P (1986).

Compounds of formula 1 have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV-related disease states in those assays.

For example, the ability of compounds of formula 1 to inhibit TNF-production in human peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are prepared from freshly taken blood or "Buffy coats"by standard procedures. Cells are plated out in RPM11640+1% foetal calf serum in the presence and absence of inhibitors. LPS (Lipopolysaccharide, 100 ng/ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere of 95% air/5%CO_2. Supernantants are tested for TNFα by ELISA (Enzyme linked immunosorbent assay) using commercially available kits.

In vivo activity in a skin eosinophilia model is determined by using the methods described by Hellewell et al, Br.J.Pharmacol. 111: 811 (1994) and Br.J.Pharmacol. 110 : 416 (1993). Activity in a lung model is measured using the procedures described by Kallos and Kallos, Int. Archs. Allergy Appl. Immunol. 73 : 77 (1984), and Sanjar et al, Br.J.Pharmacol. 99: 769 (1990).

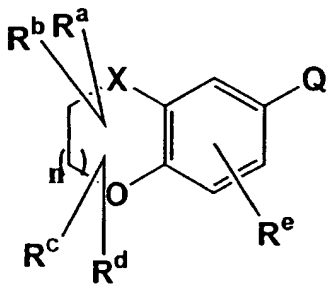
An additional lung model, which allows measurement of inhibition of the early and late-phase asthmatic responses and also the inhibition of airway hyperreactivity, is described by Broadley et al, Pulmonary Pharmacol. 7 : 311 (1994), J.Immunological Methods 190: 51 (1996) and British J.Pharmacol. 116: 2351 (1995). Compounds of the present invention showed activity in these models.

In vitro activity data of some of the compounds of the present invention against human PDE4 enzyme inhibition assay:

S. No.	Compound	IC_{50} [a]
1.	Example 1	33 mM
2.	Example 2	65 mM
3.	Example 3	75 mM
4.	Example 5	0.15 mM
5.	Example 6	0.08 mM
6.	Example 8	20 mM
7.	Example 14	35 mM
8.	Example 16	85 mM
9.	Example 30	25 mM
10.	Example 32	37 mM
11.	Example 62	17 mM
12.	**Roflumilast**	**0.01 nM**

CLAIMS

1. A compound of the general formula 1



1

wherein n represents an integer of 1 to 3; R^a, R^b, R^c or R^d may be the same or different and represent hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted cycloalkyl, polycycloalkyl, substituted or unsubstituted lower alkenyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted aromatic heterocyclic group, substituted or unsubstituted aralkyl group or two groups present on the same carbon atom among R^a, R^b, R^c, R^d may be combined to represent a optionally substituted 5-8 membered cyclic ring; or two groups present on the adjacent carbon atoms among R^a,R^b,R^c,R^d may be combined to represent a cyclic ring of 4-8 membered ; or two groups present on the adjacent carbon atoms among R^a,R^b,R^c,R^d may be combined to represent a single bond; R^e represents hydrogen, halogen, nitro, alkylamino, hydroxyl or substituted or un substituted lower alkyl, substituted or unsubstituted lower alkoxy or two moieties of R^e adjacent to each other are combined together to form a 5-6 membered cyclic ring optionally containing one hetero atom such as oxygen or nitrogen.; X represents $-N(R^f)-$, $-S(O)_m-$, -O- or $-C(R^{g1})(R^{g2})$ wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl, $-C(=O)-R^h$ or $C(=O)-O-R^h$ in which R^h is substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; R^{g1} and R^{g2} are independently hydrogen, hydroxyl,

substituted or unsubstituted lower alkyl, substituted or unsubstituted lower alkoxy groups; m is an integer of 0, 1 or 2 ; and *Q represents*

(A) a group which represents $-C(R^1)=N-O-(Y)_p-W$ wherein Y is substituted or optionally substituted lower alkyl, -C(=O), -C(=S), -C(=O)-O, or C(=O)-NH group; p is an integer of 0 or 1; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups; R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; and s is zero or the integer 1,2,3,or 4; Z is a bond, -O-, -S-, or $N(R^i)$; wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups;

(B) a group such as $-C(R^1)=C(R^j)-W$ wherein R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or $N(R^i)$ wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. groups; and s represents an integer of 0 to 4;

(C) a group $-C(R^1)(R^2)-(CHR^j)-W$ wherein R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups ; R^2 represents hydroxyl, substituted or unsubstituted lower alkoxy, $-OC(=O)-R^k$, $-OC(=O)NHR^k$, in

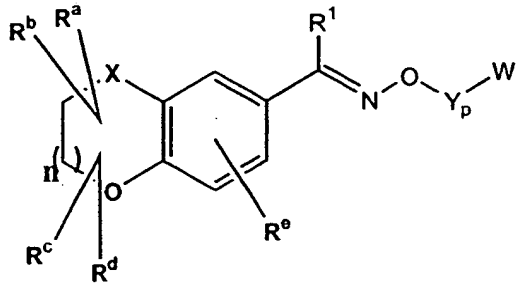
which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups ; R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or $N(R^i)$ wherein R^i represents hydrogen, substituted or unsusbstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups; s is an integer of 0 to 4; and W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups;

(D) a group $-CH(R^1)-L-W$ wherein L represents $-N(R^i)-$, S(O)r-,-O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.groups and r is an integer of 0,1 or 2 ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or $N(R^i)$ and s is an integer of 0 to 4;

(E) a group $-CONH-(CH_2)_t-Ar^2$ where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsitued cycloalkyl, substituted or unsubstituted heterocyclic groups ; their analogs, their tautomers, their regioisomers, their stereoisomers, their geometrical isomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates

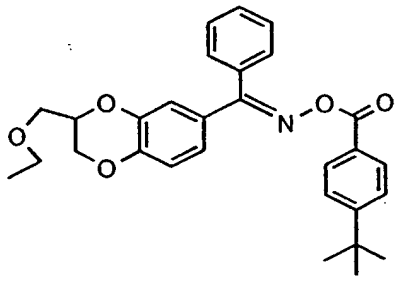
and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of.

2. A compound of the general formula,

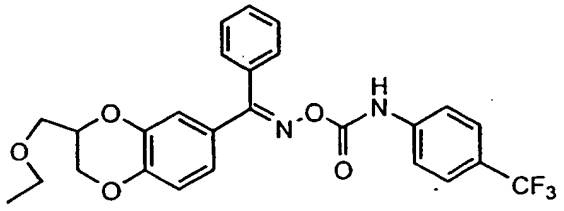


wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups, R^1 represents preferably substituted or unsubstituted aryl or heteroaryl groups, Y denotes preferably -C(=O), or -C(=O)-NH group when p = 1 and W denotes preferably substituted or unsubstituted aryl or heteroaryl groups.

3. A compound, O-(4-tert.butylbenzoyl)-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)phenyl ketoxime of the formula

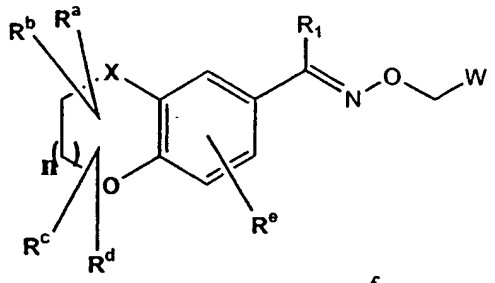


4. A compound, O-(4-trifluoromethylphenylaminocarbonyl)-(3-



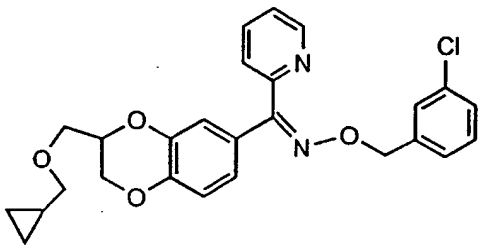
ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)phenyl ketoxime, of the formula

5. A compound of the general formula,

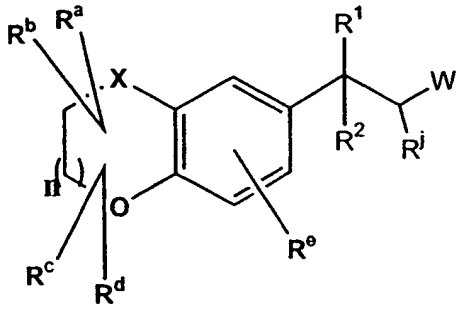


wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups, R^1 represents preferably substituted or unsubstituted aryl or heteroaryl groups and W denotes preferably substituted or unsubstituted aryl or heteroaryl or heterocyclic groups.

6. A compound, O-(m-chlorobenzyl)-1-(3-cyclopropylmethoxymethyl-2,3-dihydro-benzodioxin-6-yl)-1-(2-pyridyl) methanone oxime, of the formula

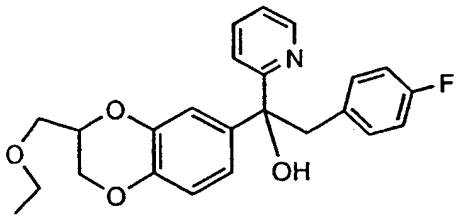


7. A compound of the general formula,

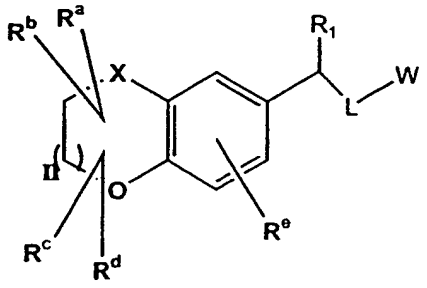


wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e and R^j are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups, R^1 represents preferably substituted or unsubstituted aryl or heteroaryl groups, R^2 denotes hydroxyl group and W denotes preferably substituted or unsubstituted aryl or heteroaryl or heterocyclic groups.

8. A compound, 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-pyridyl-1-(4-fluorobenzyl)-1-hydroxy methane, of the formula

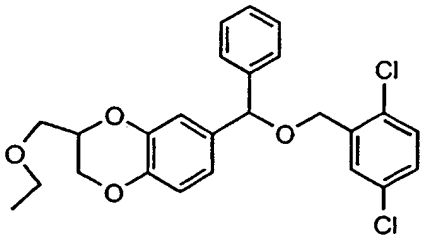


9. A compound of the general formula ,

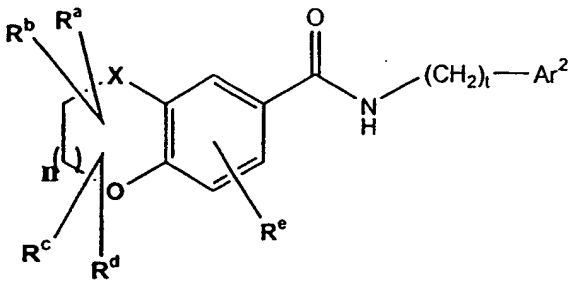


wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups, R^1 represents preferably substituted or unsubstituted aryl or heteroaryl groups, L denotes preferably oxygen or NR^i in which R^i represents hydrogen or substituted or unsubstituted lower alkyl groups and W denotes preferably substituted or unsubstituted lower alkyl or cycloalkyl or heterocyclic groups.

10. A compound, 1-[3-ethoxymethyl-2,3-dihydrobenzodioxan-6-yl]-1-phenyl-1-(2,5-dichlorobenzyloxy) methane, of the formula

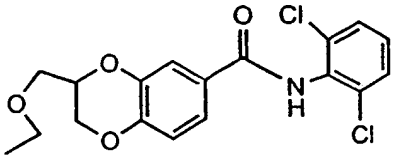


11. A compound of the general formula ,



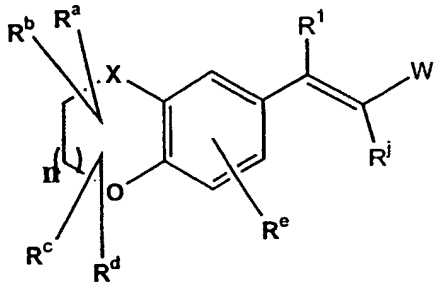
wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups and Ar^2 denotes preferably substituted aryl or hetreroaryl and substituted cyloalkyl or heterocyclic groups when t=0.

12. A compound, N-(2,5-dichlorophenyl)-3-ethoxymethyl-2,3-



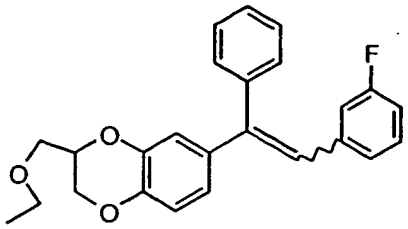
dihydrobenzodioxin-6-carboxamide, of the formula

13. A compound of the general formula,

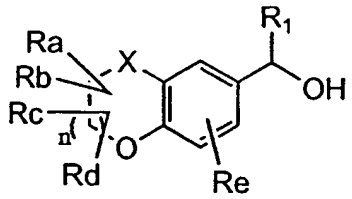


wherein X represents preferably oxygen or -N(R^f) wherein R^f is a hydrogen, substituted or unsubstituted lower alkyl group, R^a, R^c, R^d, R^e and R^j are preferably hydrogen, n = 1 or 2 , R^b preferably represents substituted lower alkyl or alkenyl groups, R^1 represents preferably substituted or unsubstituted aryl or heteroaryl groups and W denotes preferably substituted or unsubstituted aryl or heteroaryl or heterocyclic groups

14. A compound, 1-(3-ethoxymethyl-2,3-dihydrobenzodioxin-6-yl)-1-phenyl-2-(m-fluorophenyl)ethylene, of the formula

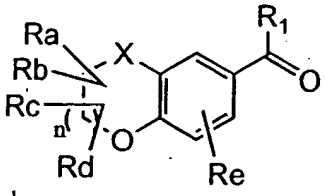


15. Novel intermediates of the formula **10**,



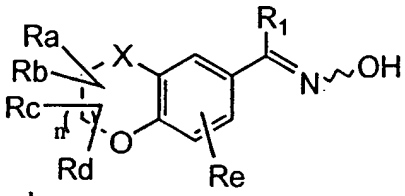
where X, R_a to R_e and R^1 have the meanings described in claim1.

16. Novel intermediates of the formula **11**,



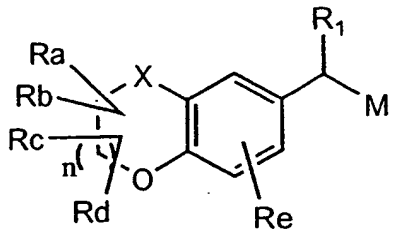
where X, R_a to R_e and R^1 have the meanings described in claim1.

17. Novel intermediates of the formula **12**,



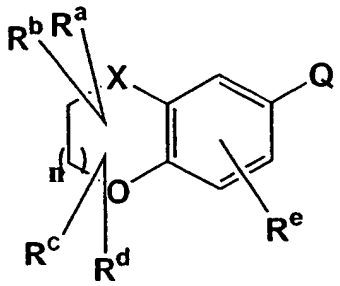
where X, R_a to R_e and R^1 have the meanings described in claim1.

18. Novel intermediates of the formula **14**



where X, R_a to R_e and R^1 have the meanings described in claim1 and M represents a leaving group such as halogen, mesylate, tosylate or triflate and the like.

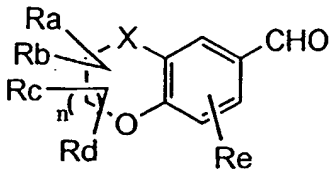
19. A process for the preparation of compounds of the general formula **1A**,



1A

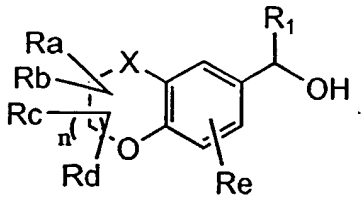
where Q is a group which represents $-C(R^1)=N-O-(Y)_p-W$ wherein Y is substituted or optionally substituted lower alkyl, -C(=O), -C(=S), -C(=O)-O, or C(=O)-NH group; p is an integer of 0 or 1; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups; R^1 is a $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl); and s is zero or the integer 1,2,3,or 4; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, the other symbols having the meanings given earlier which comprises,

(a) reacting the compound of the general formula **9** where X, R^a to R^e have the meanings described above



9

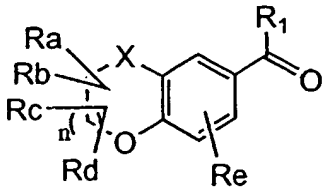
with a group $\mathbf{R^1}$**-J** where J is halogen other than fluorine and R^1 is a –(CH_2)s-Z-Ar^1 group, where Ar^1 is an hydrogen, optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl, Z is a bond, -O-, -S-, or NR^i and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted loweralkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, in the presence of alkyl lithium or Mg/ Li metal and ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxyl compounds of the general formula **10**



10

where R^1 is not a hydrogen and all the other symbols having the meanings given earlier,

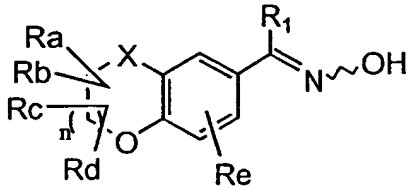
(b) reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



11

where all the symbols have the meanings given earlier

(c) reacting the novel ketone of the formula 11 with hydroxylammonium chloride in the presence of a base and a alcoholic solvent to obtain corresponding novel oxime of the formula 12

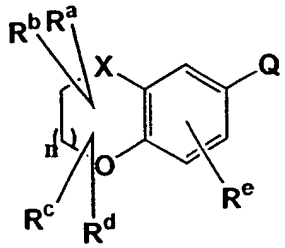


12

(d) reacting the compounds of the formula 12 with a reagent of the formula

W-G-J

where J denotes chlorine or bromine and G represents groups like $-CH_2$, C(=O), -C(=S) -OC(=O) or -NHC(=O) in the presence of a base and aprotic or ethereal solvents to provide the novel compounds of the formula 1A



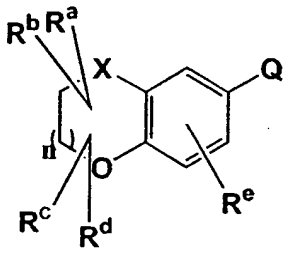
1A

where Q represents $-C(R^1)=N-O-(Y)_p-W$ where p denotes 0 or 1 and Y represents substituted or unsubstituted lower alkyl, -C(=O) or -C(=S) group, -C(=O)O group or -C(=O)NH group and X, R^a to R^e, R^1 and W have the meaning described above,

(e) if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(f) and if required further purifying the compounds of the formula by conventional methods.

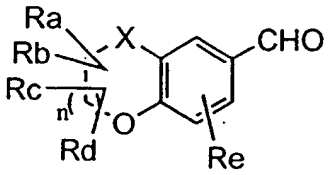
20. A process for the preparation of the compounds of the formula **1B**



1B

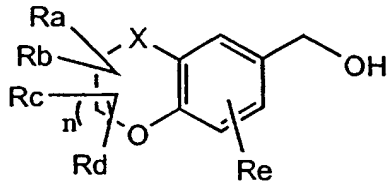
where Q represents $-CH(R^1)-L-W$ wherein L represents $-N(R^i)-$, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 represents hydrogen, which comprises,

(a) reacting the compound of the formula **9** ,



9

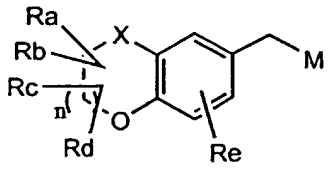
where X, R^a to R^e have the meanings described above, with a reducing agent in the presence of ethereal solvents at a temperature in the range of -10 to 25°C to get the corresponding novel hydroxyl compound of the formula **13,**



13

wherein the symbols have the meanings given earlier,

(b) converting the hydroxyl group in the compounds of the formula **13** where R^1 is hydrogen and the other symbols have the meanings described above, into a leaving group M such as halogen, mesylate, tosylate or triflate and the like, by following conventional methods known in literature to obtain the novel compounds of the formula **14,**



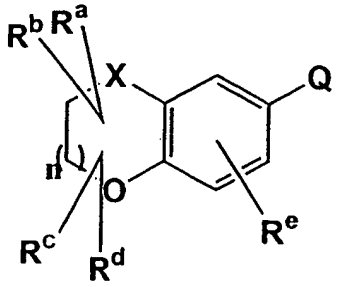
14

where all the symbols have the meanings given earlier,

reacting the novel compounds of the formula **14** with a reagent of the formula

W-L-H

where L denotes -O, -NR^i, -$S(O)_r$ wherein r represents 0 to 2, and W has the meaning given earlier , in the presence of a base and ethereal or aprotic solvent at a temperature in the range of 0 to 80 °C to get the novel compounds of the formula **1B**



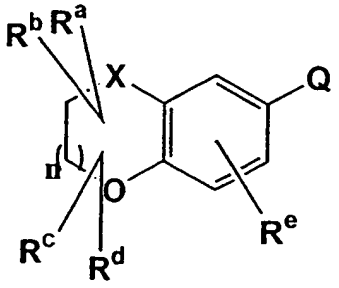
1B

where Q represents –**CH(R^1)-L-W** wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 represents hydrogen, X, R^a to R^e have the meaning described above.

(d) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(e) and if required further purifying the compounds of the formula by conventional methods.

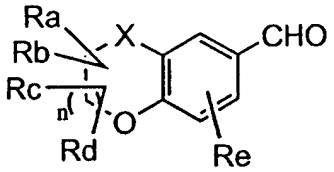
21. A process for the preparation of the compounds of the formula 1C



1C

where Q represents $-C(R^1)(R^2)-(CHR^j)-W$; wherein W is hydrogen, substituted or unsub-stituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and s is an integer of 0 to 4; R^2 represents hydroxyl, substituted or unsubstituted lower alkoxy, $-OC(=O)-R^k$, $-OC(=O)NHR^k$, in which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; which comprises,

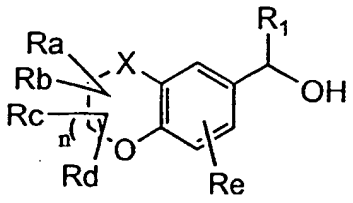
(a) reacting the compound of the formula **9**



9

where X, R^a to R^c have the meanings described above with a group $\mathbf{R^1}$-**J** where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group, where Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl ; Z is a bond, -O-, -S-, or $N(R^i)$ and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl , substituted or unsubstituted heteroaryl groups, in the presence of alkyl lithium or Mg/Li metal and an ethereal or aromatic solvents at a temperature in the range of -

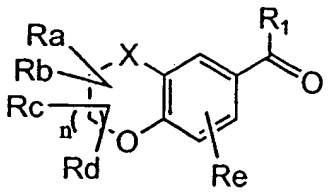
70 to 80° C to obtain the novel hydroxy compounds of the general formula **10**



10

where R^1 is not a hydrogen and all the other symbols having the meanings given earlier,

(b) reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



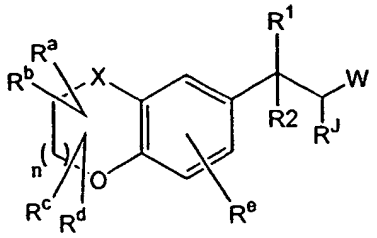
11

where all the symbols have the meanings given earlier,

(c) reacting the novel compounds of the formula **9** or **11** with a reagent

W-(CHR^j)-J

where R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups hydrogen or lower alkyl group and J represents halogen other than fluorine, in the presence of magnesium or lithium metal and ethereal or aromatic solvents at a temperature in the range of 0 to 80° C to produce the novel compounds of the formula **15**



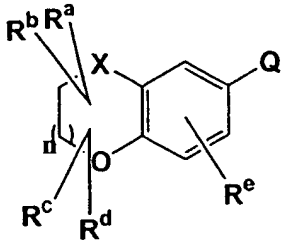
15

where R^a to R^e have the meaning given above and where R^2 represents hydroxyl group and R^j , R^1& W have the meanings given earlier,

(d) reacting the novel compounds of the formula **15** in the presence of a base and a chlorinated solvent with a reagent of the formula

W-G-J

where J denotes chlorine or bromine and G represents groups like $-CH_2$, C(=O), -OC(=O) or -NHC(=O), to produce the compounds of the formula **1C**



1C

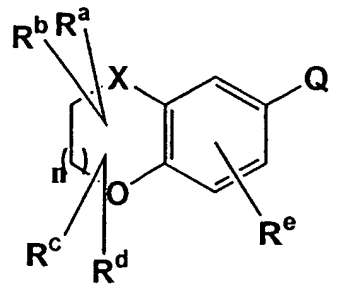
where Q denotes $-C(R^1)(R^2)-(CHR^j)-W$ wherein R^2 represents substituted or unsubstituted lower alkoxy, $-OC(=O)-R^k$, $-OC(=O)NHR^k$, in which R^k represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups ; R^j having the same meaning described in the above and X, R^a to R^e, R^1 and W have the meaning described above ,

(e) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their

pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(f) and if required further purifying the compounds of the formula by conventional methods.

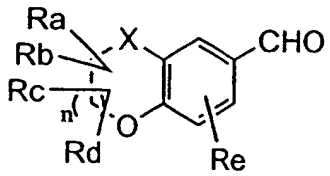
22. A process for the preparation of the compounds of the formula **1D** ,



1D

where Q represents $-C(R^1)=C(R^j)-W$ wherein W is hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group $-(CH_2)s-Z-Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i wherein R^i represents hydrogen, substituted or unsusbstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and s is an integer of 0 to 4; R^j represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl groups; which comprises,

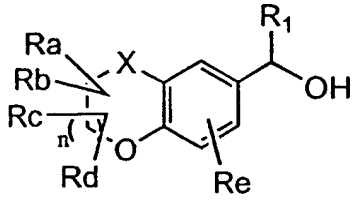
reacting the compound of the formula **9**



9

where X, R^a to R^e have the meanings described above with a group $\mathbf{R^1}$**-J** where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group,

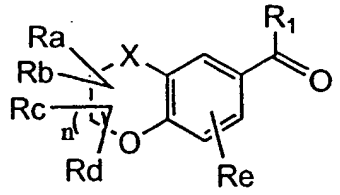
where Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl ; Z is a bond, -O-, -S-, or $N(R^i)$ and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl , substituted or unsubstituted heteroaryl groups, in the presence of alkyl lithium or Mg/Li metal and an ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxy compounds of the general formula **10** ,



10

where R^1 and all the other symbols having the meanings given earlier,

(b) reacting the novel hydroxyl compound of the formula **10** with an oxidizing agent in the presence of a chlorinated solvent to get the novel ketone of the general formula **11**



11

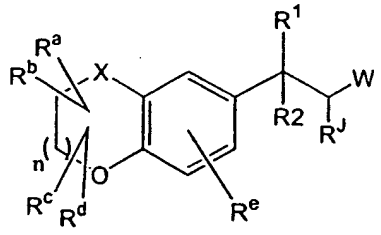
where all the symbols have the meanings given earlier,

(c) reacting the novel compounds of the formula **9** or **11** with a reagent of the formula

W-(CHR^j)-J

where R^j is having the same meaning described in the above and J represents halogen other than fluorine, in the presence of magnesium or lithium metal

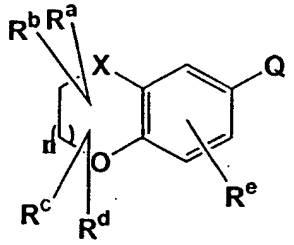
and an ethereal or aromatic solvents at a temperature in the range of 0 to 80° C to produce the novel compounds of the formula **15**



15

where R^a to R^e have the meaning given above and where R^2 represents hydroxyl group and R^J, R^1& W have the meanings given earlier

(d) reacting the novel compounds of the formula **15** with an acid in the presence of ethereal or aromatic solvent to provide the novel compounds of the formula **1D** ,



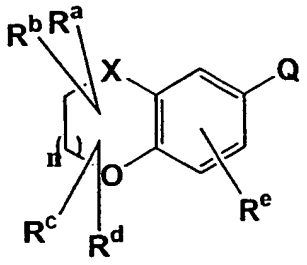
1D

and Q represents $-C(R^1)=C(R^J)-W$ where R^J denotes hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups and X, R^a to R^e, R^1 and W have the meaning described above

(e) if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them or a pharmaceutical acceptable salts there of by conventional methods,

(f) and if required further purifying the compounds of the formula by conventional methods.

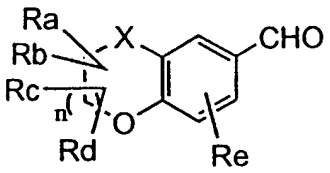
23. A process for the preparation of a compound of the general formula **1E,**



1E

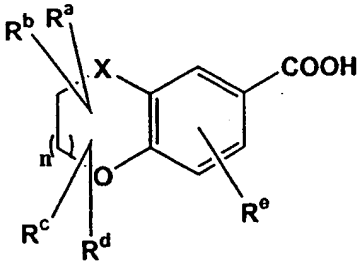
where Q represents a group -CONH-$(CH_2)_t$-Ar^2 where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups, which comprises,

reacting the compounds of the formula **9**



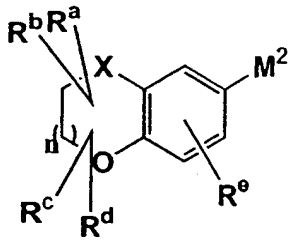
9

where X, R^a to R^e have the meanings described above with a strong oxidizing agent following conventional methods to obtain the novel compounds of the formula **16,**



16

converting the compounds of the formula **16** into the compounds of the formula **17,**

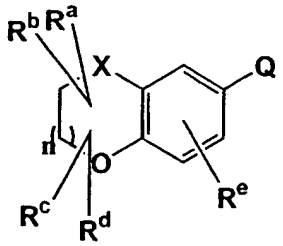


17

where M^2 is an acid chloride or a mixed anhydride such as -CO-O-CO-R^m where R^m denotes lower alkyl groups by conventional methods, reacting the novel compounds of the formula **17** with the reagent of the formula

$$Ar^2\text{-}(CH_2)_t\text{-}NH_2$$

where t is 0 to 4 and Ar^2 has the meaning described above, in the presence of a base and ethereal solvent or chlorinated solvent, an aromatic solvent or an aprotic solvent at a temperature in the range of 0 to 80°C to obtain the novel compound of formula **1E,**



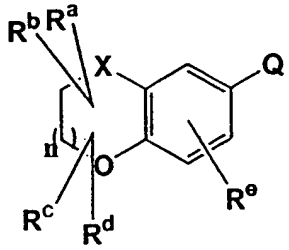
1E

where Q represents a group -CONH-$(CH_2)_t$-Ar^2 where t is 0 to 4 and Ar^2 represents substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubsituted cycloalkyl, substituted or unsubstituted heterocyclic groups and X, R^a to R^e have the meaning described above ;

(d) and if desired preparing their analogs, their tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(e) and if required further purifying the compounds of the formula by conventional methods.

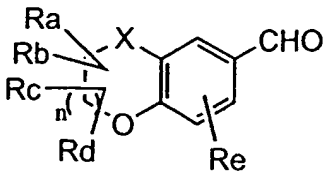
24. A process for the preparation of the compounds of the formula **1F**



1F

where Q represents **–CH(R^1)-L-W** (wherein L represents –N(R^i)-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group –(CH_2)s-Z-Ar^1 wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i and s represents an integer of 0 to 4; which comprises,

(a) reacting the compound of the formula **9** ,

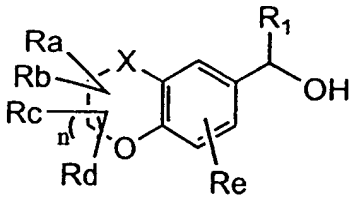


9

where X, R^a to R^e have the meanings described above, with a reagent of the formula

R^1-J

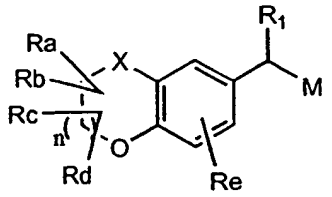
where J is halogen other than fluorine and R^1 is a $-(CH_2)s-Z-Ar^1$ group, where Ar^1 is an hydrogen, optionally substituted monocyclic or bicyclic heteroaryl, substituted or unsubstituted aryl, Z is a bond, -O-, -S-, or NR^i and s is zero or the integer 1,2,3,or 4; and R^i represents hydrogen, substituted or unsubstituted loweralkyl, substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl groups, in the presence of alkyl lithium or Mg / Li metal and ethereal or aromatic solvents at a temperature in the range of -70 to 80° C to obtain the novel hydroxy compounds of the general formula **10** ,



10

where R^1 and all the other symbols having the meanings given earlier,

(b) optionally converting the hydroxyl group in the compounds of the formula **10** into a group M where M represents amino, thio or sulfonyl group by following conventional methods known in literature to obtain the novel compounds of the formula **18,**



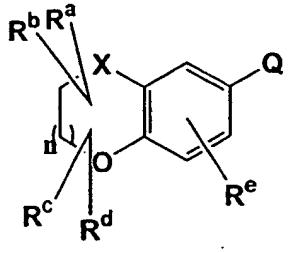
18

where all the symbols have the meanings given earlier,

(c) reacting the novel compounds of the formula 10 or 18 with a reagent of the formula

$$W\text{-}J^1$$

where J^1 denotes halogen or optionally a leaving group such as mesylate or tosylate or triflate etc., and W has the meaning given earlier , in the presence of a base and an ethereal or aprotic solvent at a temperature in the range of -20°C to 80 °C to get the novel compounds of the formula 1F



1F

where Q represents $-CH(R^1)$-L-W wherein L represents $-N(R^i)$-, S(O)r-, -O- in which R^i represents hydrogen, substituted or unsubstituted lower alkyl group, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl group ; r is an integer of 0,1 or 2 and ; W represents hydrogen, substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic groups and R^1 is a group $-(CH_2)s\text{-}Z\text{-}Ar^1$ wherein Ar^1 is hydrogen, an optionally substituted monocyclic or bicyclic heteroaryl , substituted or unsubstituted aryl; Z is a bond, -O-, -S-, or NR^i and s represents an integer of 0 to 4; and X, R^a to R^e have the meaning described above if desired preparing their analogs, their

tautomers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them.or a pharmaceutical acceptable salts there of by conventional methods,

(e) and if required further purifying the compounds of the formula by conventional methods.

25. A process as claimed in claims 19 to 24, wherein the ethereal solvents used are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like.

26. A process as claimed in claims 19 to 24, wherein the chlorinated solvent employed are selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like .

27. A process as claimed in claims 19 to 24, wherein the aromatic solvents employed are selected from benzene, toluene and the like.

28. A process as claimed in claims 19 to 24, wherein the alcoholic solvents employed are selected from methanol, ethanol, n-propanol, iso propanol, tert.butanol and the like.

29. A process as claimed in claims 19 to 24, wherein the polar aprotic solvents employed are selected from acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, and the like.

30. A process as claimed in claims 19 to 24, wherein the reaction time employed ranges from 0.5 hr to 48 hrs, preferably between 0.5 hr to 16 hrs.

31. A process as claimed in claims 19 to 24, wherein the oxidizing agents employed are selected from pyridinium chlorochromate, pyridinium dichromate, chromium trioxide, barium manganate, chromic acid, manganese dioxide, potassium permanganate and the like.

32. A process as claimed in claims 19 to 24, wherein the bases employed are selected from lithium carbonate, sodium carbonate, potassium carbonate,

cesium carbonate, sodium hydride, potassium hydride, potassium hydroxide, sodium hydroxide, lithium hydroxide, sodium methoxide, potassium tert.butoxide, n-butyl lithium and the like.

33. A pharmaceutical composition comprising the compounds of formula 1 as defined and claimed in claims 1 to 10 their analogs, their tautomers, their regioisomers, their stereoisomers, their geometrical isomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates and a pharmaceutically acceptable carrier, diluent, excipient or solvate.

34. A pharmaceutical composition as claimed in claim 33, wherein it contains one or more known drugs selected from other clinically useful anti asthma agents.

35. A pharmaceutical composition as claimed in claims 33, in the form of a tablet, capsule, powder, syrup, solution or suspension.

36. A method for inhibition of the production of tumor necrosis factor in a patient to be treated comprising administering to the patient the compound of claim 1 in an amount effective for such inhibition.

37. A method for inhibition of the production of a phosphodiesterase type 4 enzyme in a patient to be treated comprising administering to the patient the compound of claim 1 in an amount effective for such inhibition.

38. The use of the compound of claim 1, to inhibit the production of a phosphodiesterase type 4 enzyme.

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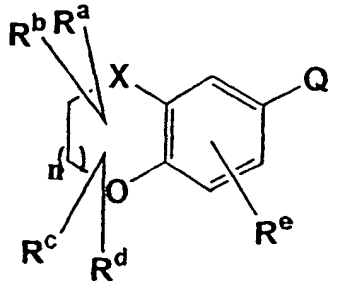
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: HETEROCYCLIC COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: A compound of the general formula (I) and method for preparing and using the compound of formula (I).



(I)

WO 02/072567 A3

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/US 02/07315

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/20 C07D405/12 A61K31/357 A61P37/00 C07D405/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3.157 674 A (L.H. WERNER) 17 November 1964 (1964-11-17) column 0; claims 11,12; examples 10,11	1,33-35
X	claims 10,11	16
A	FR 1 193 637 A (RHONE-POULENC) 4 November 1959 (1959-11-04) page 1 -page 2	1,33-35
X	page 1 -page 2	16
A	DE 15 18 042 A (MERCK) 12 June 1969 (1969-06-12) page 14 -page 16; claims	1,33-35
X	page 14 -page 16; example 4	16
A	WO 92 18494 A (CIBA-GEIGY) 29 October 1992 (1992-10-29) claims 1,9; examples 2,15,16	1,2,5,17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2002	08/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/07315

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 28 40 454 A (DR. MADAUS) 3 April 1980 (1980-04-03) page 1; claims	1,2,13, 33-37
A	GB 2 046 259 A (KYOWA HAKKO KOGYO) 12 November 1980 (1980-11-12) the whole document	1,7, 33-35
X	ALEJANDRA G. SUAREZ: "ALCL3-DMA REAGENT" TETRAHEDRON LETTERS., vol. 40, 1999, pages 3523-6, XP004162326 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 page 3523 -page 3525	16
X	V. THIÉRY ET AL.: "CONVENIENT SYNTHESIS OF 2-SUBST. 6- OR 7-ACYLATED 1,4-BENZODIOXIN" TETRAHEDRON., vol. 51, no. 9, 1995, pages 2619-28, XP002214666 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4020 examples 22A,22B	16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/07315

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 36,37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No
PCT/US 02/07315

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